Understanding antibiotic PK/PD profiles to optimize patient outcomes

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International Society of antiinfective Pharmacology

PK/PD of Anti-Infectives Study Group of the
European Society of Clinical Microbiology and Infectious Diseases

7th Asia-Pacific Respiratory Tract Infections Forum
Ho Chi Minh, Vietnam

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Disclosures

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• *Université catholique de Louvain* for personal support
• Commercial Relationships:
  – AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, Vetoquinol
• Other relationships in relation to this talk
  – Belgian Antibiotic Policy Coordination Committee,
  – Belgian Transparency and Reimbursement Committees
  – Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones
What is an anti-infective drug?

THE LANCAST, AUGUST 16, 1913.

Address in Pathology
ON
CHEMOTHERAPEUTICS:
SCIENTIFIC PRINCIPLES, METHODS, AND RESULTS.

Delivered before the Seventeenth International Congress of Medicine

BY WIRKL, GEH. OBER-MED.-RAT PROFESSOR
DR. PAUL EHRICH,
DIRECTOR OF THE ROYAL INSTITUTE FOR EXPERIMENTAL THERAPY,
FRANKFURT AM MAIN.

THE THERAPIA STERILISANS MAGNA.
The therapia sterilisans magna consists in this, that by means of one or at most two injections the body is freed from the parasites. In experiments on animals, and also in the case of a series of important maladies, this principle can be carried through in a clear and pure manner. Here, therefore, the old therapeutic remedy is applicable:

"Frapper fort et frapper vite."
A simple pharmacological concept…

The dose must be adapted to the goal…

![Graph showing concentration vs. therapeutic response with points indicating improving and worsening situations.](image-url)
In a nutshell…

The target is the bacteria = MIC

Known quantity of bacteria placed into each tube

- 0 µg/mL
- 0.25 µg/mL
- 0.5 µg/mL
- 1.0 µg/mL
- 2.0 µg/mL
- 4.0 µg/mL
- 8.0 µg/mL
- 16 µg/mL

Increasing antibiotic concentration
In a nutshell...

The target is the bacteria = MIC

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

24h later...

<table>
<thead>
<tr>
<th>Concentration (µg/mL)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Sad</td>
</tr>
<tr>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>Sad</td>
</tr>
<tr>
<td>8.0</td>
<td>Smiley</td>
</tr>
<tr>
<td>16</td>
<td>Smiley</td>
</tr>
</tbody>
</table>
What is the relationship between MIC and effect?

S. aureus

log extracellular concentration (X MIC)

change in CFU over 24h (log_{10})

oxacillin

moxifloxacin

E_{min}

E_{max}

It looks as if they are all concentration-dependent...

But here comes pharmacokinetics …

Weak concentration-dependence (max. effect) over the $C_{\text{min}} - C_{\text{max}}$ range  
→ TIME will emerge as the main parameter in vivo

$C_{\text{min}} - C_{\text{max}}$

high concentration-dependence over the $C_{\text{min}} - C_{\text{max}}$ range  
→ CONCENTRATION will emerge as an important parameter in vivo

- $C_{\text{min}}$-$C_{\text{max}}$: Principles and Practice of Infectious Diseases, 7th Ed. Mandell et al. eds., Elsevier
A further comparison: in vitro kill curves

Time kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration. (From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. Scand J Infect Dis. 1990;74:63–70.)
First conclusions

Considering their pharmacokinetics in humans

• β-lactams appear as "time-dependent" antibiotics because their serum concentrations is almost always > MICs … if you administer them several times a day (most have only short serum half-lives)

• Fluroquinolones (and aminoglycosides) are primarily "concentration-dependent" antibiotics as their bactericidal effect increases in proportion to their $C_{\text{max}}$/MIC ratio.
Moving to actual conditions of use

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

Graph:
- X-axis: Time (h)
- Y-axis: Concentration
- $C_{\text{max}}$
- $\text{AUC}_{24h}$
PK/PD in animals: $\beta$-lactams

1. For $\beta$-lactams, time > MIC is the only key index for efficacy

PK/PD in animals: fluoroquinolones

2. For fluoroquinolones, both $\text{AUC}_{24h}/\text{MIC}$ and $\text{C}_{\text{max}}$ emerge as key indices

Correlation of PK/PD Indices with Efficacy of Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice
(W.A. Craig – ISAP workshop – ICAAC 2009)
What is an $\text{AUC}_{24\text{h}}$?

$\text{AUC}_{24\text{h}} = \text{dose} / \text{clearance}$
How do I get a larger $AUC_{24h}$?

$AUC_{24h} = \frac{\text{dose}}{\text{clearance}}$

By increasing the dosage.
How do I get a larger \( AUC_{24h} \) ?

\[ AUC_{24h} = \text{dose} / \text{clearance} \]

```
Concentration
```

By increasing the half life (decreasing the clearance)
What is an $AUC_{24h}$ / MIC?

Ratio between
- $AUC_{24h}$ (dose / clearance)
- MIC
What is an $AUC_{24h}$ / MIC?

$AUC_{24h}$ / MIC

MIC high $\rightarrow$ Low $AUC_{24h}$ / MIC

high MIC

$\begin{array}{c}
\text{Concentration} \\
\text{Time (h)}
\end{array}$
What is an AUC$_{24h}$?

MIC low $\rightarrow$ high AUC$_{24h}$/MIC

Concentration

Time (h)

low MIC

23 March 2013
7th RTI Forum, Ho Chi Minh, Vietnam
PK/PD in animals

Immune status influences the magnitude of the PK/PD index required for efficacy

Relationships between mortality at the end of therapy and the 24 h AUC/MIC of fluoroquinolones with multiple pathogens (left panel) in different animal models (mostly immunocompromised) and with S. pneumoniae in non-neutropenic models (right panel).

AUC$_{24h}$/MIC in patients

Time (days of therapy) to bacterial eradication versus AUC/MIC in severely ill patients treated with ciprofloxacin. The three groups differed significantly (P < 0.005).

Forrest et al AAC (1993) 37:1073-81
AUC\textsubscript{24h}/MIC and prevention of resistance

Change in susceptibility of S. aureus after exposure to fluoroquinolones

$C_{\text{max}}$ and the "Mutant Prevention Concentration" (MPC) …

\[ \text{MIC}_{99} = 0.8 \]

"Classic" bactericidal effect

Surviving bacteria

Concentration

Poorly sensitive organisms…

Elimination of resistant organisms

MPC $10 = 9$

Dong 	extit{et al}: AAC 1999; 43:1756-1758
"Mutant Prevention Concentration …"

Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

MIC\textsubscript{99} = 0.8

MPC\textsubscript{10} = 9

Dong \textit{et al}; AAC 43:1756-1758
"Window" where selection of mutants/resistants may take place …

Putting all together for fluoroquinolones

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

- peak / MIC > 10

If you are interested in global effect …

- $\text{AUC}_{24h} / \text{MIC}: 30 \text{ to } 125$
Be practical… a short exercise

• 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
  - $\text{MIC}_{\text{max}}$: 0.5-1.5
- Peak [mg/l]: 4.5
  - $\text{MIC}_{\text{max}}$: ~0.5

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

MIC data: J. Verhaegen et al., ECCMID 2003
Similar values in 2009 (Vanhoof, ECCMID 2009)
The problem of the wrong breakpoints...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit</th>
<th>Breakpoints (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( C_{\text{max}} ) in mg/L</td>
<td>( \text{AUC}_{24\ h} ) (mg x h/L)</td>
<td>Efficacy</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
<td>0.1–0.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
<td>0.2–0.7</td>
</tr>
</tbody>
</table>

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute)

The EUCAST 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 Efficacy$^1$</th>
<th>EUCAST breakpoints</th>
</tr>
</thead>
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<tr>
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## EUCAST breakpoints

### S. pneumoniae

<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>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin¹</td>
<td>0.12</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin²</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Nalidixic acid (screen)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Norfloxacin (screen)</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin³</td>
<td>0.12</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

*This is close to PK/PD breakpoints*

These (and more) data are available at no cost from EUCAST and can be accessed freely on EUCAST website [www.eucast.org](http://www.eucast.org). Note: EUCAST recommendations are frequently updated but the latest versions is always available on EUCAST web site.
**EUCAST breakpoints**

**S. pneumoniae**

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<td>0.12</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin²</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Nalidixic acid (screen)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Norfloxacin (screen)</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin³</td>
<td>0.12</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

1. Wild type *S. pneumoniae* are not considered susceptible to ciprofloxacin and are therefore categorised as intermediate.

A. The norfloxacin disk diffusion test can be used to screen for fluoroquinolone resistance. **See Note B.**

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### EUCAST breakpoints

**S. pneumoniae**

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<th>Zone diameter breakpoint (mm)</th>
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<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.12</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Levofoxacin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Nalidixic acid (screen)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Norfloxacin (screen)</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.12</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

2. The breakpoints for levofloxacin relate to high dose therapy.

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### EUCAST breakpoints

**S. pneumoniae**

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<tr>
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<th>Zone diameter breakpoint (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S ≤</td>
<td>R &gt;</td>
<td>S ≥</td>
</tr>
<tr>
<td>Ciprofloxacin(^1)</td>
<td>0.12</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Levofloxacin(^2)</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.5</td>
<td>0.5</td>
<td>5</td>
</tr>
<tr>
<td>Nalidixic acid (screen)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Norfloxacin (screen)</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Ofloxacin(^3)</td>
<td>0.12</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

3. Wild type *S. pneumoniae* are not considered susceptible to ofloxacin and are therefore categorised as intermediate.

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Use of PK/PD protects against resistance of *S. pneumoniae* to moxifloxacin: experience in the community in Belgium

*S. pneumoniae* susceptibility to moxifloxacin in Belgium

From data of a **national collection**
- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S.pneumoniae* from clinically-confirmed CAP)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 448 in 2008)
- Data available yearly for 1999 through 2008
- [http://www.iph.fgov.be](http://www.iph.fgov.be)

But you can (and must) use your own data...

C. Zhao et al. / Diagnostic Microbiology and Infectious Disease 73 (2012) 174–181

Table 1

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Antimicrobial agents</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%S^a</td>
<td>MIC_{50}</td>
<td>%S^a</td>
<td>MIC_{50}</td>
<td>%S^a</td>
<td>MIC_{50}</td>
<td>%S^a</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levofloxacin</td>
<td>89.9</td>
<td>97</td>
<td>1</td>
<td>98.7</td>
<td>1</td>
<td>97.8</td>
</tr>
<tr>
<td></td>
<td>Moxifloxacin</td>
<td>93.3</td>
<td>0.38</td>
<td>98</td>
<td>0.125</td>
<td>100</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Youning Liu et al.

Table 4: Antimicrobial susceptibility of 63 S. pneumoniae isolates obtained in the study

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>% of isolates</th>
<th>MIC (μg/ml)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible</td>
<td>Intermediate</td>
<td>Resistant</td>
<td>MIC_{50}</td>
<td>MIC_{90}</td>
<td>Range</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>93.7</td>
<td>0.0</td>
<td>6.3</td>
<td>1</td>
<td>2</td>
<td>0.5–16</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>93.7</td>
<td>0.0</td>
<td>6.3</td>
<td>0.25</td>
<td>0.5</td>
<td>0.125–4</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>95.2</td>
<td>3.2</td>
<td>1.6</td>
<td>0.125</td>
<td>0.25</td>
<td>0.064–4</td>
</tr>
</tbody>
</table>
I was not alone…

not too long ago …

and to clinical practice

G. Drusano  W.A. Craig  J.J. Schentag
Questions?

There are
NO STUPID QUESTIONS
or stupid answers.