Asian PK/PD Educational Workshop

PK/PD and resistance
or
How shall we tackle with the future…
Why would PK/PD be important for the prevention of resistance?

- rate and intensity of the bactericidal effects
- minimizing the potential for acquisition and/or emergence of mechanisms of resistance
- dealing with populations of decreased susceptibility

Dead bacteria never get resistant
How you kill might be important...
Creating a safety margin...
Why would PK/PD be important for the prevention of resistance?

- rate and intensity of the bactericidal effects
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Dead bacteria never get resistant
PK/PD and resistance: importance of the rate of bactericidal effect

- less time for the bacteria
  - to acquire mechanisms of resistance
  - to build (or let the host build) barriers that will impair antibiotic access to its target
- better cooperation with the mechanism of resistance of the host
The 1993 study of Forrest *et al.* shows that a 24h AUC/MIC ratio for ciprofloxacin causes a slow clearance of bacteria.

A 1998 study by the same group (Thomas JK, *et al.*, AAC 42:521–7) shows that the risk of getting resistant is related to a 24h AUC/MIC ratio of < 100.
Resistance and 24h AUC / MIC \textit{in vitro}

Resistance of \textit{S. aureus} 201 to three quinolones related to AUC$_{24}$/MIC

$r^2 = 0.9$

Firsov ICAAC-2002
Why would the rate of bactericidal effect be critical?

A simple application of Darwin’s concepts ...

Selection pressure

- gene
- enzyme / nucleoprotein
- function
Why would the rate of bactericidal effect be critical?

A simple application of Darwin’s concepts ...

No antibiotic = no pressure

gene

enzyme / nucleoprotein

function
Why would the rate of bactericidal effect be critical?

A simple application of Darwin’s concepts ...

No living bacteria = no possibility of pressure

gene

enzyme / nucleoprotein

function
Why would the rate of bactericidal effect be critical?

A simple application of Darwin’s concepts ...

A lot of ill-killed bacteria = a lot of possibility of pressure

gene

enzyme / nucleoprotein

function
Why would PK/PD be important for the prevention of resistance?

- rate and intensity of the bactericidal effects
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How you kill might be important ...
The **bacterial** efflux pumps may defeat a good PK ...

- by decreasing the intrabacterial concentration of the antibiotic and resulting in subinhibitory concentrations and thereby favouring the possibility of mutations or acquisition of mechanisms of resistance
- by allowing the development of multiple resistance
Efflux and selection of resistance to FQ

A certain serum AUC and a certain serum peak will determine the drug concentration at the target level which may prevent the selection of first and second mutation resistsants
Efflux and selection of resistance to FQ

Gyrase/ Topoisomerase
Efflux and selection of resistance to FQ

Efflux pumps will reduce the concentration at the level of the target and thereby favor the selection of target mutants!

Gyrase/ Topoisomerase
Efflux and selection of resistance

Frequency of Levofloxacin-resistant mutants in Pseudomonas aeruginosa

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<tr>
<th>Pump status</th>
<th>LVX MIC</th>
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<tr>
<td>WT</td>
<td>0.25</td>
<td>$2 \times 10^7 - 4 \times 10^7$</td>
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Wild P. aeruginosa show both a relatively high MIC and a high frequency of resistant mutants

Lomovskaya et al, AAC (1999) 43:1340-1346
**Efflux and selection of resistance**

Frequency of Levofloxacin-resistant mutants in *Pseudomonas aeruginosa* if deleting the efflux pump operons

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The MIC falls to low values ...
**Efflux and selection of resistance**

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<td>0.25</td>
<td>$2 \times 10^6$</td>
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<tr>
<td>$\triangle$ mexAB-oprM;$\triangle$ mexCD-oprJ</td>
<td>0.015</td>
<td>$1 \times 10^9$</td>
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<td>$\triangle$ mexAB-oprM;$\triangle$ mexCD-oprJ;$\triangle$ mexEF-oprN</td>
<td>0.015</td>
<td>$&lt;1 \times 10^{11}$</td>
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**AND the selection of mutants in FQ target becomes undetectable when ALL pumps are disrupted**
Efflux and multi / cross-resistance in pathogenic bacteria

1 bacteria → several pumps → multiresistance

1 pump → several classes of antibiotics → crossresistance

1 class of antibiotics → several pumps → efficacy of inhibitors?
Most frequent antibiotic-pumps in procaryotes (1/2)

- **Resistance Nodulation Division (Gram - )**

**TOPOLOGY**

**MECHANISM**

**ANTIBIOTICS**

- tetracyclines
- fluoroquinolones
- erythromycin
- rifampicin

- β-lactams
- fluoroquinolones
- fusidic acid

- chloramphenicol

- aminoglycosides
Most frequent antibiotic-pumps in procaryotes (2/2)

- **Major Facilitator Superfamily** (Gram + and -)

### TOPOLOGY

12 TMS

- NH₂
- COOH

14 TMS

- NH₂
- COOH

### MECHANISM

- Proton antiport

### ANTIBIOTICS

- Tetracyclines
- Fluoroquinolones
- Macrolides
- Lincosamides
- Rifampicin
- Pristinamycin
- Chloramphenicol
- Aminoglycosides
Effect of fluoroquinolone concentration on selection of resistant mutants of *Mycobacterium bovis BCG* and *Staphylococcus aureus*

Dong YZ, Zhao XL, Domagala & Drlica-K


• *Mycobacterium bovis BCG* and *Staphylococcus aureus*

• increasing concentrations of fluoroquinolones
  – a sharp drop, followed by a plateau and
  – a second sharp drop.
Bactericidal activity of FQs against *M. bovis*

The plateau region correlates with the presence of first-step resistant mutants.

Mutants are not recovered at concentrations above those required for the second sharp drop, thereby defining a Mutant Prevention Concentration (MPC).
Effect of fluoroquinolone concentration on selection of resistant mutants of Mycobacterium bovis BCG and Staphylococcus aureus
Dong YZ, Zhao XL, Domagala & Drlica-K

The mutant prevention concentration (MPC) is about 10 times larger than the MIC99 for most FQ

BUT, a C-8-methoxy group lowers the MPC for N-1-cyclopropyl fluoroquinolones
Role of the C8-methoxy in decreasing MPC

Bactericidal activity of FQs against *Mycobacterium bovis*

Fraction of survivors vs. FQ concentration

- **MIC** 99: 0.25 vs. 0.8
- **MPC** 10: 0.9 vs. 9
- **MPC/MIC**: 3.6 vs. 12

Dong *et al*; AAC 43:1756-1758
Peak concentrations as a tool to prevent emergence of resistance (MPC): using “PK / PD acceptable” MICs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>C\textsubscript{max} (mg/L)</th>
<th>“PK/PD Bkpt” (mg/L)</th>
<th>expect. MPC</th>
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<tr>
<td>norfloxacin</td>
<td>800</td>
<td>2.4 *</td>
<td>0.2</td>
<td>~ 2.4</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>2.4 *</td>
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</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>3-4.5 *, +</td>
<td>0.4</td>
<td>~ 4.8</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>5-6 *, +</td>
<td>0.8</td>
<td>~ 9.6</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>4.5 *</td>
<td>0.4</td>
<td>~ 1.4</td>
</tr>
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* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®
* first dose to equilibrium
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+ first dose to equilibrium

This is the $C_{\text{max}}$ you'd like to obtain.
Why would PK/PD be important for the prevention of resistance?

- rate and intensity of the bactericidal effects
- minimizing the potential for acquisition and/or emergence of mechanisms of resistance
- dealing with populations of decreased susceptibility

Creating a safety margin...
# 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>
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<td>moxifloxacin</td>
<td>400</td>
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How to apply this in a given country (Belgium)?

Levofloxacin 500 mg
1X/day

- AUC [(mg/l)xh] 47
- peak [mg/l] 5
- $\text{MIC}_{\text{max}}$ AUC < 0.5
- $\text{MIC}_{\text{max}}$ peak < 0.5

You are left with 20% of non-covered bacteria!!

MIC data: J. Verhaegen et al., 2001
Why do we fear rapid emergence of large resistance to levofloxacine in Belgium?

Resistance to FQ occurs easily and rapidly by:
- single-step mutation
- express. of efflux pumps

=} increase of MICs by 1 or 2 dilutions

One dilution increase will be enough to cause
~ 40 % of strains to have MICs > 0.5 mg/L for levofloxacine
Why would telithromycin be potentially interesting in a given area (example = Belgium)?

Evolution of resistance of S. pneumoniae to erythromycin

References:
- Laboratory for pneumococci, Louvain
  - Erythromycin R = Clarithromycin R = Roxithromycin R = Azithromycin R
  - ~ Miocamycin R
Pharmacodynamics of telithromycin
(as based on FDA submission; april 2001)

<table>
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<tr>
<th>Organism</th>
<th>( \text{MIC}_{90} )</th>
<th>( \frac{C_{\text{max}}}{\text{MIC}_{90}} )max</th>
<th>( \frac{\text{AUC}<em>{24h}}{\text{MIC}</em>{90}} )max</th>
</tr>
</thead>
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<tr>
<td>S. pneumoniae</td>
<td>&lt; 0.008 - 0.25</td>
<td>7.6</td>
<td>33.2</td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>&lt; 0.015 - 0.06</td>
<td>31.6</td>
<td>138</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>2.0 - 4.0</td>
<td>0.475</td>
<td>2.075</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>0.12</td>
<td>15.8</td>
<td>69.1</td>
</tr>
<tr>
<td>L. pneumophila</td>
<td>0.03 - 0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>0.03 - 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>0.25</td>
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Activity will be good for \( \text{MIC} \leq 0.25 \text{ mg/L} \), but may become problematic for higher MICs

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/
But why do we also fear a rapid resistance to telithromycin in Belgium?

\[ \text{PK/PD limit of activity (0.25 mg/L)} \]

**MIC\textsubscript{90} for Ery-s strains**: < 0.06 ...

**But MIC\textsubscript{90} for Ery-r strains**: 0.25-0.5 ...

This is where we are now ... 

Dosage → Serum concentration varying over time → Concentration at the site of infection → Therapeutic effects

Concentration in non-target tissues → Toxic effects

Think not only in the short but also in the long range ...
This is where Regulators and many others wish us to go ...

Dosage

Serum concentration varying

Concentration at the site of infection

Therapeutic effects

Think not only in the short but also in the long range ...

EMEA Discussion Paper on Antimicrobial Resistance

London, 27 July 2000
CPMP/EWP/2655/99

POINTS TO CONSIDER ON PHARMACOKINETICS AND PHARMACODYNAMICS IN THE DEVELOPMENT OF ANTIBACTERIAL MEDICINAL PRODUCTS