PK/PD to fight resistance

- Eradicate
  - Abnormal bacteria
  - Mutations
  - Efflux pumps
- Mutation-Preventing Concentration
- Breakpoint values for $T > MIC$
- and in practice …

With the support of Wallonie-Bruxelles-International
Mutant selection: role of antibiotics...

High selection pressure

gene

enzyme / nucleoproteine

fonction

Poorly active antibiotics...

The worse you can do is to not kill bacteria!!!

therefore, eradicate...

...
NOTES

Abnormal Morphology of Bacteria in the Sputa of Patients Treated with Antibiotics

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Received 13 January 1982/Accepted 2 April 1982

Filaments of Klebsiella pneumoniae were observed by Gram stain in the sputum of a patient with a respiratory infection who was treated with half the usual dose of cefazolin. Identical filaments were observed in vitro when this strain was incubated with subminimum inhibitory concentrations of cefazolin. Large gram-positive cocci containing multiple cross walls were observed by electron microscopy in the sputum of a patient with a respiratory infection who was treated with ampicillin and gentamicin. Antibiotic administration was suspended the night before the sputum was obtained. The ultrastructure of these cocci was very similar to the ultrastructure of Staphylococcus aureus incubated with subminimum inhibitory concentrations of cephaloridine or oxacillin. It was suspected that the low dose of cefazolin and the intermittent therapy with ampicillin resulted in a subminimum inhibitory concentration of antibiotic in the respiratory tract which induced the abnormal morphology of the bacteria observed in the sputum of both patients. The presence of abnormal forms of bacteria in the specimen of a patient, rather than in the culture of a specimen, has clinical significance.
Pictures of abnormal bacteria upon exposure to subinhibitory concentrations ... 

Less potent antibiotics are more prone to loose their activity against mutated targets …

Example for a « weak » quinolone: Two mutations make it clinically inefficient …
In contrast, more potent antibiotics remain active even on first-step mutants…

Example for a « strong » quinolone: two mutations do not prevent it to be active…

MIC

Limit of Clinical susceptibility

2nd mut.

1st mut.

wild.

Strong FQ
Efflux ...

Bacteria with efflux pump...

Gyrase/ Topoisomerase

Targets are exposed to too low concentrations
Efflux and mutations cooperate to surpass the susceptibility limit...

- Limit of susceptibility
- MIC

- No efflux
- ciprofloxacin
- efflux

1st mut.
2nd mut.
sauv.

- wild.
4 reasons to eradicate …

• Killed bacteria do not mutate anymore … (simple application of Darwin’s concepts…)

• If they are killed, they cannot contaminate their neighbors … (basic principle for epidemiology actions …)

• After all, if Pasteur is right (and he is…), don’t we need to eliminate the pathogen to cure ? (physiopathological basis of infectious diseases…)

• Don’t you wish that you patient recovers more quickly and defenitely ? (a satisfied patient will be faithfully)
Mutation-Preventing Concentration (MPC)...

Example: bactericidal activity of FQs vs *Mycobacterium bovis*

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

« classical » bactericidal activity

\[ \text{MPC}_{10} = 9 \]

Elimination of first-step mutants

Dong et al; AAC 43:1756-1758
**Mutation-Preventing Concentration (MPC)**...

- **MIC**$_{99} = 0.8$ (Concentration inhibiting the growth of most organisms)
- **MPC**$_{10} = 9$ (Concentration required to prevent the selection of first-step mutants)

Dong *et al.*; AAC 43:1756-1758
Mutant Selection Window (MSW)...
Mutant Selection Window (MSW)...

- **MIC**
- **MPC**
- **MSW**

- Eradication of first-step mutants
- Selection of first-step mutants
- No therapeutic effect

Time after the administration

Mutant Selection Window (MSW)...

- Will kill everything
- Will cause resistance
- No effect
PK/PD and MPC: stay above the MPC to avoid mutant selection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (unitary)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
<th>observed MPC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>400</td>
<td>1.2 *</td>
<td>~ 2.0</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>2.4 *</td>
<td>~ 2.0</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>200</td>
<td>1.5-3 *, +</td>
<td>~ 5.0</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>5-6 *, +</td>
<td>~ 9.6</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>4.5 *</td>
<td>~ 1.4</td>
</tr>
</tbody>
</table>

* Data from registration files
# literature data;
+ first dose and equilibrium

Due to the presence of C8-methoxy
for levofloxacin, serum concentrations remain > MIC during 20 h
BUT are always < MPC
Of pneumococci

High risk for selection of resistance!
In contrast, for moxifloxacin, serum concentrations remain above the MPC of pneumococci during at least 14 h.

Lower risk for selection of resistance.
Exercise with fluoroquinolones...

Prevention of resistance and efficacy:

- peak / MIC > 12
  and/or > MPC

- AUC / MIC > 100
  (non fully immunocompetent patients)
AUC\textsubscript{24h} / MIC = 125 \textbf{AND} Peak / MIC > 10 as parameters defining the limit of susceptibility to FQ

<table>
<thead>
<tr>
<th>FQ</th>
<th>Dose (mg/24h)</th>
<th>AUC/MIC</th>
<th>peak / CMI</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>1200</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>200</td>
<td>0.1-0.2</td>
<td>0.15 - 0.2</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.5</td>
<td>0.4 - 0.5</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* AUC for 24 h doses
‡ C\textsubscript{max} for recommended unitary doses
AUC<sub>24h</sub> / MIC = 125 AND Peak / MIC > 10 as parameters defining the limit of susceptibility to FQ

<table>
<thead>
<tr>
<th>FQ</th>
<th>Dose (mg/24h)</th>
<th>PK/PD breakpoint (mg/L) based on</th>
<th>CLSI Bkpt (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AUC/MIC * peak / CMI ‡</td>
<td></td>
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<td>norfloxacin</td>
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* AUC for 24 h doses
‡ C<sub>max</sub> for recommended unitary doses
Application to pneumococci from Belgium

Levofoxacin 500 mg
1X/day
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
  - MIC\textsubscript{max} < 0.5

Moxifloxacin 400 mg
1X/day
- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
  - MIC\textsubscript{max} < 0.5

MIC data: J. Verhaegen et al., 2003
Application to pneumococci from Belgium

Levofloxacin 500 mg
1X /day
- AUC [(mg/l)xh] 47
- peak [mg/l] 5
  - MIC\(_{\text{max}}\) < 0.5

in 2003, about 40 % of Belgian isolates had MIC higher than the PK/PD breakpoint if levofloxacin is used at a daily dose of 500 mg

MIC data: J. Verhaegen et al., 2003
Why do we fear a rapid emergence of resistance to levofloxacin in pneumococci in Belgium?

If a one-dilution reduction in susceptibility occurs compared to 2003 values, 95% of strains would have an MIC higher than the PK/PD breakpoint. Except if the dose is doubled...

Levofloxacin 500 mg  
1X/day  
• AUC [(mg/l)xh] 47  
• peak [mg/l] 5  
- \( \text{MIC}_{\text{max}} < 0.5 \)
Application to pneumococci in Belgium ...

in 2003, all the Belgian strains had an MIC below the PK/PD breakpoint if moxifloxacin is used at a daily dose of 400 mg

**Moxifloxacin** 400 mg
1X/day

- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5
  - $\text{MIC}_{\text{max}} < 0.5$

**MIC data:** J. Verhaegen et al., 2003
Can we do the exercise for *P. aeruginosa*?

MIC distributions for *P. aeruginosa*

PK/PD limit for levo 500 mg: more than 60% of the so-called "susceptible" strains are out of the range...

J. van Eldere, 2003

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<table>
<thead>
<tr>
<th>MIC distributions for <em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>oflox</td>
</tr>
</tbody>
</table>
Distribution des CMI de *Ps. aeruginosa*

Levo 1000 mg: 30 % of the so-called "susceptible" strains are still out of the range...

J. van Eldere, 2003

Can we do the exercise in Belgium?
Can we do the exercice in Belgium?

Distribution des CMI de *Ps. aeruginosa*

Cipro 1200 mg:
85% of the so-called "susceptible" strains have MIC below the PK/PD breakpoint.
Rational basis of quinolone choice…

- Knowledge of local epidemiology
  - MIC distributions …
- Calculation of the PK profile necessary to obtain an optimal activity on > 90% of the target organisms (in terms of AUC and peak)
  - consider a safety margin (MPC …)
- Comparison between proposals …