Pharmacodynamics of antibiotics as a means to improve and curb the emergence of resistance

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www.facm.ucl.ac.be  www.isap.org

2d JSP International Conference
Why pharmacodynamics?

- Rising resistance and correlation with antibiotic use …
- What is pharmacodynamics of antibiotics
- What can we do with that…
  - for the clinical laboratory and the clinician …
  - for the health authorities
- Can pharmacodynamics help in preventing (or slowing down the emergence of) resistance ? …
- Can we also reduce health care costs ? …
Resistance is the problem ... the example of the *S. pneumoniae* in Belgium

* all β-lactams (= penicillins, cephalosporins, ...)

Belgian Reference Laboratory for pneumococci, Leuven, 2000
Overuse is also the problem …
the example of beta-lactams in Europe

Risk of resistance to β-lactams among invasive isolates of *Streptoccus pneumoniae* regressed against outpatient sales of beta-lactam antibiotics in 11 European countries
• resistance data are from 1998 to 1999; antibiotic sales data 1997.
• DDD = defined daily doses

How can you be "better"?

- be globally efficacious
  ➔ pharmacodynamics (PK/PD)

- avoid selection of resistance
  ➔ "mutant prevention concentration"
What is Pharmacokinetics / Pharmacodynamics (PK/PD) ?

• Pharmacokinetics: what the body does to the drug
  ➔ absorption, distribution, serum and tissue levels elimination, …

• Pharmacodynamics (of AB): what the drug does to the bacteria
  ➔ static vs. bactericidal effect, rate of kill, eradication, prevention of resistance…. 

- E_{max}
- time to E_{max}
- prevention of relapses
- maintenance of susceptibility
The problem as seen from a question of the FDA...

Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...
And the answer by the European Agency for Evaluation of Medicinal Products (EMEA)

EMEA Discussion Paper on Antimicrobial Resistance

POINTS TO CONSIDER ON PHARMACOKINETICS AND PHARMACODYNAMICS IN THE DEVELOPMENT OF ANTIBACTERIAL MEDICINAL PRODUCTS
What are "Pharmacodynamic indices"?

- all drugs have pharmacokinetic properties that describe the way the body handles them
  - antibiotics are no exception …
  - you need to consider the $C_{\text{max}}$ and the clearance (that will result in a given half-life) to describe the drug exposure

- a drug needs to bind to its target to act …
  - antibiotics are again no exception, but the target is the bacteria …
  - the antibiotics can be studied in vitro to look at the extent of their action at increasing concentrations (like the binding of a ligand to its receptor in conventional pharmacology). This is drug pharmacodynamics…
Pharmacokinetics $\Rightarrow$ Pharmacodynamics...

Pharmacokinetics
conc. vs. time

Pharmacodynamics
conc. vs. effect

PK/PD
effect vs. time

H. Derendorf,
ISAP PK/PD workshop 2002
Example of a pharmacodynamic relationship

Emin

Emax

MIC

And what if we put pharmacokinetics?

And what if we put pharmacokinetics?

- **C_{min} - C_{max}**
  - Low concentration dependency
  - High concentration dependency

From Pharmacokinetics to Pharmacodynamics of AB ...
A simple dynamic model ...

\[ T_{1/2} = 0.693 \times \frac{V}{Cl} \]

Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999
Pharmacodynamics: the basic question …

Which antibiotics are in clinically meaningful conditions?

- time-dependent
- AUC
- peak-dependent
Available antibiotics can be divided in 3 groups:

- Time-dependent (T > MIC)
- AUC/MIC-dependent
- Both AUC/MIC and peak/MIC-dependent
Antibiotics Group # 1
(after W.A. Craig, 2000; revised 2002 and 2003)

1. Antibiotics with time-dependent effects and no or little persistent effects

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams</td>
<td>time above the MIC</td>
<td>Maximize the exposure time</td>
</tr>
</tbody>
</table>
How long should you stay above the MIC?

Moderate infections:
- cefotaxime
- neutropenic mice
- K. pneumoniae
- lung infection

Serious infections:

\[ R^2 = 94\% \]

40% of infections can be treated with 40% of the MIC.
Do all β-lactams have similar PK/PD properties?...

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 (□).

- same shape of dose response
- diff. In T > MIC for a static effect (penicill. > carbap.)
- diff $E_{max}$ (penicill. < carbap.)

Dosing amoxycillin for respiratory tract infections in Belgium

Sensitivity of *S. pneumoniae* to amoxycillin

**Dose and schedule**

- **T > CMI = 50%**
- 1000 mg, 3 x / j
- 500 mg, 3 x / j
- 500 mg, 2 x / j

**MIC data:** J. Verhaegen et al., 2001
Antibiotics Group # 2

(after W.A. Craig, 2000; revised 2002 and 2003)

2. Antibiotics with time-dependent effects, no or little influence of concentration, but marked, persistent effects

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycopeptides</td>
<td></td>
<td>optimize the amount of antibiotic</td>
</tr>
<tr>
<td>tetracyclines</td>
<td>AUC / MIC</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>
Antibiotics Group # 3  
(after W.A. Craig, 2000; revised 2002 and 2003)

3. **Antibiotics with concentration-dependent bactericidal activity and prolonged persistent effects (post-antibiotic effects)**

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td><strong>Peak and AUC / MIC</strong></td>
<td>optimize the peak and the amount of antibiotic</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketolides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aminoglycosides: get a peak!

1. Appropriate mode of administration
   - IV route

2. Calculation of the necessary peak value
   - minimal peak: \( \text{MIC} / 8 \)

3. Calculation of the adequate dosage
   - peak = \( \text{dosis} / Vd \)
   - \( \text{dosis} = \text{peak} \times Vd \)
   - \( \text{dosis} = \text{MIC} \times 8 \times Vd \)
Aminoglycosides: why a peak?

Aminoglycosides are concentration-dependent drugs in the clinically meaningful concentration range ...
Aminoglycosides: why a peak?

Clinical efficacy is linked to peak/MIC ratio

Fluoroquinolones: get a peak and an AUC!

increase the amount administered, in order to optimize AUC/MIC

and peak/MIC

should be $> 125$ *

should be $> 10$

Get both a peak and a AUC!!
Why an AUC / MIC > 125 for fluoroquinolones ...

AUC / MIC is one parameter ...

Forrest et al., AAC, 1993
What do you mean by PEAK / MIC > 10 and AUC / MIC > 100

\[ \text{AUC}_{24h} = \frac{\text{dose}}{\text{clearance}} \]
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)
Is 125 good for all ??

The saga of *S. pneumoniae* ...
How to optimize the AUC / MIC ratio?

\[ \text{AUC} = \text{dosis} / \text{Cl} \]

- Adjust the daily dose
  - target AUC

- Adapt the number of administrations
  - pharmacokinetics of the drug
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
A clinical algorithm (follow.) ...

Success?

no

re-evaluate
• the dosage
• the therapeutic scheme
• the antibiotic class based on PK/PD properties

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

yes

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
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- Can we also reduce health care costs ? …
Can we use this to set better breakpoints?

The next slides describe the EUCAST procedure for harmonizing European breakpoints and reach rational values.

European Committee for antibiotic susceptibility testing
1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT ≤ X mg/L)

![Graph showing Ciprofloxacin / Escherichia coli antimicrobial wild type distributions.](https://via.placeholder.com/150)

Epidemiological cut-off: WT ≤ 0.064 mg/L

- **MIC**: Epidemiological cut-off: WT ≤ 0.064 mg/L
- **4416 observations (6 data sources)**
- **Clinical breakpoints**: S ≤ 0.5 mg/L, R > 1 mg/L
3. Existing national clinical breakpoints are compared

4. Pharmacokinetic data are collected and evaluated

Pharmacokinetic data are collected from various sources, particularly data from patients. If the data allow it and if necessary, population pharmacokinetic models are developed.

These are necessary for PK/PD analyses, including Monte Carlo simulations.

5. Pharmacodynamic data are evaluated

The PK/PD index value resulting in optimal outcome is determined from:
- in vitro data
- animal studies
- clinical trials

The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated.
Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens.

For ciprofloxacin 500 mg q12h oral, the PK/PD breakpoint is $S = 0.5$ mg/L.

For levofloxacin 500 mg q24h oral, the PK/PD breakpoint is $S = 1$ mg/L.
5. Clinical data relating outcome to MIC-values, wild type and resistance mechanisms are assessed in relation to the tentative breakpoint.

"Minimum requirement for S-category" is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug."
6. PK/PD breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin.

- Splitting the wild type must be avoided to permit reproducible susceptibility testing!
- ... thus only a breakpoints of 2 mg/L was acceptable but with a footnote that this was based on high dose therapy.
7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments. When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:
   - EUCAST general committee
   - Expert committees (Neisseria, Anaerobes, others)
   - Pharmaceutical industry, AST device manufacturers
   - Others via EUCAST website

9. Rationale document prepared and published on website
How to implement EUCAST breakpoints

- The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using the one of the European national systems will gradually adhere to the European breakpoint system.

- Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions (local and national surveillance, EARSS, etc).

- Systems for automated susceptibility testing can be set up with EUCAST MIC breakpoints.

- Through an agreement between EMEA, EFPIA and EUCAST new antimicrobials will be given breakpoints through EUCAST as part of the registration process. The SPC for these drugs will contain only EUCAST breakpoints.
EUCAST websites are found at

www.eucast.org

The EUCAST websites are accessed via www.eucast.org

This is a section of the official ESCMID website giving details of all EUCAST activities including
- constitution
- organization
- committee member lists
- meetings
- EUCAST documents
- clinical MIC breakpoint tables
- MIC distributions for wild type bacteria and fungi
- epidemiological MIC cut-off values
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- Can we also reduce health care costs?...
Mutant Prevention Concentration …

$\text{MIC}_{99} = 0.8$

"Classic" bactericidal effect

Elimination of resistant organisms

Dong et al; AAC 43:1756-1758

Surviving bacteria

concentration

$\text{MPC}_{10} = 9$
Mutant Prevention Concentration ...

Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

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

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

Dong et al; AAC 43:1756-1758
"Window" where selection of mutants/resistants may take place ...

Which are the MPC values compared to 
- MIC for *S. pneumoniae* 
- $C_{\text{max}}$ for a standard dose?

<table>
<thead>
<tr>
<th>Molecule</th>
<th>MIC</th>
<th>MPC</th>
<th>$C_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>levoflox. (500 mg)</td>
<td>1</td>
<td>8</td>
<td>$\approx 6$</td>
</tr>
<tr>
<td>moxiflox. (400 mg)</td>
<td>0.25</td>
<td>1</td>
<td>$\approx 4$</td>
</tr>
</tbody>
</table>

Adapted from D. Croisier, 2005, Bondeau et al., 2001, and Hansen et al, 2003
So, let us accept values with some degree of precaution

If you wish to prevent resistance

- peak / MIC > 10
  (which covers the MPC)

If you believe your patient is not a healthy mouse …

- \( \text{AUC}_{24h} / \text{MIC} > 100 \)
**A proposal for PK/PD based-breakpoints for fluoroquinolones...**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage&lt;sup&gt;a&lt;/sup&gt;</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&lt;sub&gt;max&lt;/sub&gt; in mg/L total/free (dose)</td>
<td>AUC&lt;sub&gt;24 h&lt;/sub&gt; (mg × h/L) total/free</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
</tr>
</tbody>
</table>

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And what about health care costs?

Pharmacoeconomics

**Economic**
- cost minimization
- cost benefit
- cost effectiveness
- cost utility

**Humanistic**
- quality of life
- patient's preference
- patient's satisfaction

Pharmacoeconomics of antibiotics is still largely underdeveloped outside the USA (but US-based models cannot easily be applied);

However, comparisons identifying differences in
- amount of money needed to reach a given (better?) clinical outcome;
- expenses related to the same (or better) quality of life and patient's satisfaction;
may already suggest interesting avenues for further fine-tuning therapeutic guidelines.

Rational bases for the choice of an antibiotic

• Know your LOCAL epidemiology
  ▶ obtain MIC distributions from your microbiologists…

• know the PK profile of the drugs you consider to purchase
  ▶ aim at obtaining > 90 % efficacy against the organisms of interest (AUC, peak, time above MIC) with a standard dosage, …

• include a safety margin (MPC …)

• Compare products on that basis first …

• Remember that
  • no antibiotic (if possible) is the best…
  • but that treatment failures (when treatment is needed) cost a lot …
Here is where you will find more information ...

www.facm.ucl.ac.be

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A. Spinewine, Pharm.
S. Carryn, Pharm.
H. Chanteux, Pharm.
H. Servais, Pharm.
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A. McGowan, MD
X. Zao, PhD
V. Firsov, MD
S. Zinner, MD
A. Dalhoff, PhD
...

www.isap.org

These slides will be available on http://www.facm.ucl.ac.be