Pharmacodynamics of antibiotics: Correlation between kinetics and activity

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Pharmacodynamics of antibiotics: Correlation between kinetics and activity

- Rising resistance and correlation with antibiotic use …
- Did we use antibiotics in a rational way? …
- What is pharmacodynamics and how can it help you? …
- Can we prevent (or slow down the emergence of) resistance? …
- Can we also reduce health care costs? …
Resistance is the problem …

- macrolides
- tetracyclines
- penicillin* intermediate
- penicillin* full resistant

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

1/3 patients

1/5 patients

Belgian Reference Laboratory for pneumococci, Leuven, 2000
Overuse is also the problem …

Risk of resistance to β-lactams among invasive isolates of *Streptococcus 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….
The problem as seen from a question of the FDA...

**Figure 2. TROVAFLOXACIN vs Staphylococcus aureus**

(N = 458)

Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...

And what about those ones?

Same dose ??
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 ➔ Pharmacodynamics...

**Pharmacokinetics**
conc vs time

**Pharmacodynamics**
conc vs effect

**PK/PD**
effect vs time
Example of a pharmacodynamic relationship

Emin

Emax

MIC

MIC = Minimum Inhibitory Concentration

Emax = Maximum effect

Emin = Minimum effect

Cmax = Maximum concentration

Δ log CFU (24 h - 0 h) = Change in log Colony Forming Units from 24 hours to 0 hours

log extracellular concentration (X MIC)
And what if we put pharmacokinetics?

Emin

E_{\text{max}}

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

MIC

And what if we put pharmacokinetics?

**C_{min} - C_{max}**

- **Low concentration dependency**
- **High concentration dependency**

From Pharmacokinetics to Pharmacodynamics of AB …

- **Pic**: Peak / MIC
- **AUC / MIC**: Area Under the Curve / Minimum Inhibitory Concentration
- **Time > MIC**: Time above the Minimum Inhibitory Concentration
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 time- and peak-dependent in clinically meaningful conditions?
Available antibiotics can be divided in 3 groups:
## 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>

**PK/PD parameter:**
- **Time above:** refers to the duration for which the concentration of the antibiotic is above the minimum inhibitory concentration (MIC)
How long should you stay above the MIC?

- Moderate infections: 40% of cefotaxime, neutropenic mice, K. pneumoniae, and lung infection
- Serious infections: 100%
Do all $\beta$-lactams have similar PK/PD properties?

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

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 (□).
Dosing amoxycillin for respiratory tract infections in Belgium

Sensitivity of *S. pneumoniae* to amoxycillin

Dose and schedule for T > CMI = 50 %

1000 mg
3 x / j

500 mg
3 x / j

500 mg
2 x / j

CMI

S

I

R

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>Peak and AUC / CMI</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 dose
   - peak \( = \text{dosis} / V_d \)
   - dosis \( = \text{peak} \times V_d \)
   - dosis \( = \text{MIC} \times 8 \times V_d \)
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

Relationship between the maximal peak level/MIC ratio and the rate of clinical response. Vertical bars represent SE values.

From Moore et al., J. Infect. Dis. 155 (1987)
increase the amount administered, in order to optimize AUC/MIC should be $> 125$ *
and peak/MIC should be $> 10$

Get both a peak and a AUC!!

Fluoroquinolones: get a peak and an AUC!

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIC</td>
<td>Concentration after peak</td>
</tr>
</tbody>
</table>

* indicates optimized values.
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

AUC$_{24h}$ = dose / 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 ...

The saga of S. pneumoniae ...

non-neutropenic

neutropenic

PD of antibiotics: correlation between kinetics and activity

Tunis - 18-04-06
How to optimize the AUC / MIC ratio?

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

- Adjust the daily dosage
  - target AUC

- Adapt the number of administrations
  - pharmacokinetics of the drug
Mutant Prevention Concentration …

![Graph showing the relationship between concentration and surviving bacteria]

- $\text{MIC}_{99} = 0.8$
- "Classic" bactericidal effect
- Poorly sensitive organisms…
- Elimination of resistant organisms
- $\text{MPC}_{10} = 9$

Dong et al; AAC 43:1756-1758
Mutant Prevention Concentration ...

Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

Surviving bacteria

MIC_{99} = 0.8

MPC_{10} = 9

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

Mutation selection window

Time after administration

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 ...

- $AUC_{24h} / MIC > 100$
A proposal for PK/PD based-breakpoints for fluoroquinolones...

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage(^a)</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit of sensitivity ((\mu g/ml)) for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(C_{max}) in mg/L total/free (dose)</td>
<td>(AUC_{24, h}) (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>

PK/PD in action …

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

**Moxifloxacin** 400 mg
1X / jr
- AUC [(mg/l)xh]  48
- peak [mg/l]    4.5
→ MIC$_{\text{max}}$  < 0.5

MIC data: J. Verhaegen et al., 2003
A clinical algorithm ...

Pathology and epidemiology

Knowledge or "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.
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 …
Please, act ...

Plan national pour préserver l'efficacité des antibiotiques

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