Pharmacodynamics of antibiotics: Correlation between kinetics and activity

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www.isap.org
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, ...)

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...

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

And what about those ones ?
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

PD of antibiotics: correlation between kinetics and activity
Tunis - 18-04-06
Example of a pharmacodynamic relationship

And what if we put pharmacokinetics?

**Emin**

**Emax**

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

**MIC**
And what if we put pharmacokinetics?

Low concentration dependency

High concentration dependency

\[ C_{\text{min}} - C_{\text{max}} \]
From Pharmacokinetics to Pharmacodynamics of AB …

![Diagram showing concentration over time with various pharmacokinetic parameters like Peak / MIC, AUC / MIC, and Time > MIC.]

PD of antibiotics: correlation between kinetics and activity

Tunis - 18-04-06
A simple dynamic model ...

\[ \text{Inflow} = \text{Clearance} \]

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

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

Which antibiotics are

• time-
• AUC
• peak-

dependent

in

clinically meaningful

conditions?
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?

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

**C**

- 40%

$R^2 = 94\%$

**Moderate infections**

- **Serious infections**

$\log_{10}$ cfu per lung at 24 hours vs. Time above MIC (%)

Log$_{10}$ cfu per lung at 24 hours

0 20 40 60 80 100

0 5 10

PD of antibiotics: correlation between kinetics and activity

Tunis - 18-04-06

18
Do all β-lactams have similar PK/PD properties?...

- same shape of dose response
- diff. $\ln T > \text{MIC}$ for a static effect (penicill. > carbap.)
- diff $E_{\text{max}}$ (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 ($\Delta$), cephalosporins ($\bigcirc$), and carbapenems ($\blacksquare$).
Dosing amoxycillin for respiratory tract infections in Belgium

Sensitivity of *S. pneumoniae* to amoxycillin

- **Dose and schedule for** $T > CMI = 50\%$
  - 1000 mg $3 \times / j$
  - 500 mg $3 \times / j$
  - 500 mg $2 \times / j$

**Cumulative % of strains**

- Cumulative % of strains for amoxycillin resistance:
  - 100%
  - 50%
  - 25%
  - 0%

**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 tetracyclines macrolides linezolid streptogramins</td>
<td>AUC / MIC</td>
<td>optimize the amount of antibiotic</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
   - \( \text{peak} = \frac{\text{dosis}}{V_d} \)
   - \( \text{dosis} = \text{peak} \times V_d \)
   - \( \text{dosis} = \text{MIC} \times 8 \times V_d \)
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 *

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* ...

- **non-neutropenic**
  - Emax at 30 ...
  - Emax at 125 ...

- **neutropenic**
  - Emax at 30 ...
  - Emax at 125 ...
How to optimize the AUC / MIC ratio?

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

- Adjust the daily dose 
  ~ target AUC
- Adapt the number of administrations 
  ~ pharmacokinetics of the drug
**Mutant Prevention Concentration** …

- **MIC**<sub>99</sub> = 0.8
- "Classic" bactericidal effect
- Poorly sensitive organisms…
- Elimination of resistant organisms
- **MPC**<sub>10</sub> = 9

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

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

Concentration which will inhibit the majority of the organisms

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

Concentration needed to prevent the selection of resistant organisms

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

Time after administration

concentration

MPC

MSW

MIC

Mutation selection window

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.</td>
<td>1</td>
<td>8</td>
<td>$\approx 6$</td>
</tr>
<tr>
<td>(500 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>moxiflox.</td>
<td>0.25</td>
<td>1</td>
<td>$\approx 4$</td>
</tr>
<tr>
<td>(400 mg)</td>
<td></td>
<td></td>
<td></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</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</td>
<td>AUC&lt;sub&gt;24 h&lt;/sub&gt; (mg x h/L)</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_{max} < 0.5

Moxifloxacin 400 mg
1X / jr
• AUC [(mg/l)xh] 48
• peak [mg/l] 4.5
→ MIC_{max} < 0.5

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

Pathology and epidemiology

Knowledge or our “educated” suspicion of the causative agent

Local MIC data

Is the organism probably highly susceptible?

no

yes

Use common dosage but with attention to PK/PD

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

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 …