Merging systems pharmacology with PK/PD analysis to enhance drug discovery: the case of novel antibiotics

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with ideas and data borrowed from colleagues at the
• International Society of Antiinfective Pharmacology (ISAP),
• European Committee for Antibiotic Susceptibility Testing (EUCAST)
• European Study Group of Pharmacodynamics/Pharmacokinetics (ESPAG)
What is it all about?

• Is there a crisis with antibiotics?
  – Resistance is growing, but …
  – New compounds are less and less reaching the market

• How applying a systems pharmacology approach can lead to enhanced quantitative drug discovery and development

• How PK/PD can prevent the emergence and spreading of resistance

• Using novel antimicrobials as an example of how an integrated approach can lead to more informed decision making
The antibiotic crisis *

1. Resistance

* A pictorial view using 4 paintings of Van Gogh (who stayed briefly in Belgium when moving from Holland to France) and selected Belgian and International data
Are antibiotics following a path to madness?

discovery in soil bacteria and fungi

1928 - …
Are antibiotics following a path to madness?

and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics

1950 – 1980 …
Are antibiotics following a path to madness?

and the US General Surgeon told us that the fight was over

1970 ...
Are antibiotics following a path to madness?

But...
Extent of resistance of *P. aeruginosa*
(International data – EUCAST breakpoints)

The hidden risk of therapy (at the corner of your street …)

In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou\textsuperscript{a,1}, Sylviane Carbonnelle\textsuperscript{a,2}, Laëtitia Avrain\textsuperscript{a,b}, Narcisa Mesaros\textsuperscript{a,3}, Jean-Paul Pirnay\textsuperscript{c}, Florence Bilocq\textsuperscript{c}, Daniel De Vos\textsuperscript{c,d}, Anne Simon\textsuperscript{e}, Denis Piérard\textsuperscript{f}, Frédérique Jacobs\textsuperscript{g}, Anne Dediste\textsuperscript{h}, Paul M. Tulkens\textsuperscript{a,4}, Françoise Van Bambeke\textsuperscript{a}, Youri Glupczynski\textsuperscript{i}

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\textsuperscript{g} Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium
\textsuperscript{h} Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium
\textsuperscript{i} Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium
Do you remain effective while treating?

- D0: initial isolate
- DL: last isolate obtained
- individual values with geometric mean (95% CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

a $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

Message: for all antibiotics, we see global increases of MIC during treatment
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The original process of discovery and assessment

From the point of view of human benefit, never was a Nobel prize so justifiably awarded as was the award to Selman Waksman for the discovery of streptomycin and other antibiotics produced from *Streptomyces spp.* Waksman and his talented team (many of whom went on to make important antibiotic discoveries in their own right) developed the concept of systematic screening of microbial culture products for biological activity, a technology which has provided the foundation of the antibiotic industry, and for this alone his name should rank high in any pantheon of microbiology.

J. Davies: In Praise of Antibiotics, ASM News
And it remains like that for long ...

identification

sensitivity $\rightarrow$ S - I - R

by static techniques
Why do we need S - I - R ?

To be honest, I always wondered …
An easy time …

MIC (µg/ml)

serum concentration

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32

Good !!
Becoming bad, but not for the microbiologist

Simple answer!

MIC (µg/ml)

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32

serum concentration

Good !!

Bad !!
But today ...

No longer so easy...

serum concentration

May be?
PK/PD of antibiotics

- in vitro
- animal data
- clinical implementation
- resistance
Simple response to an antimicrobial

an example with ceftobiprole and S. aureus (one strain)

Simple response to an antimicrobial

an example with ceftobiprole and S. aureus (2 strains)

Response to an antimicrobial: the model

an example with ceftobiprole and *S. aureus* (2 strains)

![Graph showing the response to an antimicrobial with ceftobiprole and *S. aureus* (2 strains)]

Response to an antimicrobial: a first model
an example with ceftobiprole and S. aureus (multiple strains)

How can this first model be exploited?

Bactericidal vs. Static

old vs. new

bimodal A vs B

inhibitor of degradation (intracellular)
Special models: intracellular bacteria

Special models: intracellular breakpoint

Moving to humans (via animals)
What is the relationship between MIC and effect?

But here comes pharmacokinetics …

Weak concentration-dependence (max. effect) over the $C_{\text{min}}$–$C_{\text{max}}$ range

⇒ TIME will emerge as the main parameter in vivo

C$_{\text{min}}$–C$_{\text{max}}$

High concentration-dependence over the $C_{\text{min}}$–$C_{\text{max}}$ range

⇒ the time is less important than the actual concentration

- $C_{\text{min}}$–$C_{\text{max}}$: Principles and Practice of Infectious Diseases, 7th Ed. Mandell et al. eds., Elsevier
Conclusions so far ...

• Contrary to most beliefs, *all* antibiotics are concentration-dependent (like any other drug);

• **but** it is all about at which serum concentration $E_{\text{max}}$ will be obtained and how large it is (compared to untreated controls) ....

• If $E_{\text{max}}$ is small and obtained at a low concentration/MIC ratio (relative to what you could reach in serum), all what you are left with is time ... and you get *in vivo* a time-dependent antibiotic (viz. $\beta$-lactams, vancomycin, ...)

→ BEWARE ! If the MIC rises, you will need to increase the concentration to reach your (weak) $E_{\text{max}}$ or to use low breakpoints if wishing to avoid clinical failures (viz. cephalosporins ...) ...
You can test this in vitro

Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999
Ad you can even mimic compartments

- Membranes (hollow fibers)
- Dialyzers (artificial kidneys)

Adapted from M.N. Dudley, ISAP / FDA Workshop, 1999
The clinical classification of antibiotics *

- **primarily time-dependent**
  (maximal effect at low concentration/MIC ratio and no post-antibiotic effect)
  - β-lactams / flucytosine  
    - favour time > MIC

- **primarily C\text{max} dependent**
  (effect progressing over the clinically achievable concentrations AND marked post-antibiotic effect)
  - aminoglycosides  
    - favour C\text{max} / MIC
  - fluoroquinolones

- **primarily AUC\text{24h}-dependent**
  (effect progressing modestly over clinically achievable concentrations; significant post-antibiotic effect; half-lifes > 4h)
  - most other antibiotics and fluoroquinolones  
    - favour total daily dosage

* assuming human pharmacokinetics and susceptible strains
The story of β-lactams in neutropenic mouse *

* creating distinct $C_{\text{max}}$, AUC and $T>\text{MIC}$ profiles by manipulating the schedule of administration
W. Craig, Madison, WI (several publications)
But how much time above MIC is necessary?

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

**Static dose?**

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

- 40%
- $R^2 = 94\%$

**100 % - Maximal effect?**
Here is a proposal ...

<table>
<thead>
<tr>
<th>Log (_{10}) cfu per lung at 24 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time above MIC (%)</td>
</tr>
</tbody>
</table>

- **40%** Moderately severe infection in a non-immunosuppressed patient
- **100%** Severe infection in an immunosuppressed patient
But there are variation of PK in individuals...

Concentration-time profile of a
beta-lactam in volunteers
$V_d = 20\, \text{L},\, k_a = 1.2\, \text{h}^{-1},\, k_e = 0.3\, \text{h}^{-1}$

Unlike the Belgian 400 m run team, we are not all (almost) equal
What is, indeed, a standard patient?
Variation of PK in individuals...

Concentration-time profile of a beta-lactam in patients with a simulation with a coefficient var. of 20%
Monte Carlo Simulations and target attainment rate for “$fT > \text{MIC}$” (40 %)

Temocillin (6-methoxy-ticarcillin) 2 g every 12h

Figure 2. Probabilities of target attainment of temocillin (as obtained with the Monte Carlo simulation: solid line, median value; dotted lines, 95% confidence interval) for the currently registered treatment (2 g every 12 h), using the pharmacokinetic data of the six patients treated according to this dosage and schedule in this study (twice daily group). The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a percentage) during which free serum levels remain above the corresponding MIC. The horizontal dotted line indicates the 40% $fT > \text{MIC}$ limit achieving a bacteriostatic effect and survival for penicillins in animal models with Gram-negative bacteria. The highest MIC at which this target will be obtained is shown by the vertical arrows (arrow with solid line, median; arrow with dotted line, 95% probability).

But you may like to be 4 x above the MIC …

Figure 2 Relationship between concentration of ceftazidime and kill rate

The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

The problem with the fluoroquinolones
... and the link to resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical daily dosage</th>
<th>Typical PK values</th>
<th>Proposed PK/PD upper limit</th>
<th>Breakpoints (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
<td>$\text{AUC}_{24\text{h}}$ (mg $\times$ h/L) total/free</td>
<td>Efficacy $^b$</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>800 mg</td>
<td>1.4/1.1 (400 mg PO)</td>
<td>14/11</td>
<td>0.1–0.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1000 mg</td>
<td>2.5/1.75 (500 mg PO)</td>
<td>24/18</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>400 mg</td>
<td>4/3 (400 mg PO)</td>
<td>40/30</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500 mg</td>
<td>4/2.8 (500 mg PO)</td>
<td>40/28</td>
<td>0.3–0.9</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td>3.1/1.8 (400 mg PO)</td>
<td>35/21</td>
<td>0.2–0.7</td>
</tr>
</tbody>
</table>

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.nccl)

Mutant Prevention Concentration …

"Classic" bactericidal effect

Surviving bacteria

concentration

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

Elimination of resistant organisms

poorly sensitive organisms…

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

Dong et al: AAC 1999; 43:1756-1758
Mutant Prevention Concentration …

Concentration which will inhibit the majority of the organisms

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

Surviving bacteria

Concentration needed to prevent the selection of resistant organisms

$\text{MPC}_{10} = 9$

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

PK/PD 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 Efficacy</th>
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<td>$C_{\text{max}}$ in mg/L total/free (dose)</td>
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EUCAST breakpoints

### EU in action …

**European Medicines Agency**

**Standard Operating Procedure**

<table>
<thead>
<tr>
<th>Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST</th>
<th>Document no.: SOP/H/3043</th>
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<tr>
<td>Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST</td>
<td>Effective Date: 14 February 2005</td>
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<tr>
<td>PUBLIC</td>
<td>Review Date: 14 February 2007</td>
</tr>
<tr>
<td>Supersedes: N/A</td>
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<tr>
<td>Prepared by</td>
<td>Approved by</td>
</tr>
<tr>
<td>Name: Bo Aronsson</td>
<td>Name: Agnès Saint Raymond</td>
</tr>
<tr>
<td>Signature: On file</td>
<td>Signature: On file</td>
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<tr>
<td>Date: 10 Feb 05</td>
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</tbody>
</table>

1. **Purpose**
   
   To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

**EMEA and EUCAST have set up an agreement that makes EUCAST responsible for defining breakpoints for new molecules proposed for registration in Europe.**

**EUCAST breakpoints will be accepted by EMEA and put into the "Summary of Product Characteristics", which is part of legal documents accompanying the marketing authorization in EU.**
I was not alone…

not too long ago …

G. Drusano  W.A. Craig

1998

EMA

1999

ICAAC 2012
52nd ICAAC – Sept. 9-12 – San Francisco

since 1999
… and again this year

and to clinical practice