Pharmacodynamics: the methods

- In vitro models
- Animal models
- Clinical studies
- Population studies

With the support of Wallonie-Bruxelles-International
Pharmacodynamics: the methods

"un peu de tout …"
In vitro dynamic models

- Dilution models
- Diffusion models
- Hybrid models
- ‘Physiologic models’
- Intracellular models

Adapted from J. Mouton, 4th ISAP Educational Workshop, 2001
Dilution models: a simple, useful system ...

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

Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999
Diffusion models

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

Adapted from M.N. Dudley, ISAP / FDA Workshop, 1999
Some models can be very complex
The goal is to mimic potentially useful and achievable serum concentration variations.
Why *in vitro* dynamic models ...

- The goal is to establish **basic** relationships between drug exposure (PK) and effect (PD)
  - PK/PD parameters for efficacy to apply across species, models, for combinations, etc...
  - Basis of dosage in phase II trials

- Limitations:
  - Experimental conditions (laboursome; contamination; …)
  - Usually only 1 or 2 days (effects ‘fade’ after 12-24 h)
  - Absence of host factors (incl. protein binding and metabolism)
  - …
Animal models

- neutropenic mouse
- rabbit (endocarditis)
- rat, guinea pig, ...

The main advantage is the possibility to explore a VERY large array of dosing regimens so as
- **dissociate PK covariables** \( (C_{\text{max}} \text{ vs AUC} \ldots) \)
- **explore the PK “conditions of failure”**
Dissociating PK covariables:
see what are $C_{\text{max}}$, time above MIC and AUC
with a once-a-day (qd) schedule of a given dose ...

Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999
Now see what are $C_{\text{max}}$, time > MIC and AUC/MIC if increase the dose without changing the schedule

Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999
But see how $C_{\text{max}}$, time > MIC and AUC/MIC become dissociated if the SAME DAILY dose is given with a different schedule (here: divided in 3 administrations) …

Adapted from F. O. Ajayi, ISAP-FDA Workshop, 1999
A typical animal model to establish which PK parameter is associated with efficacy

- Use neutropenic murine thigh-and lung-infection models
- Evaluate 20-30 different dosing regimens (5 different total doses given at 4-6 different dosing intervals)
- Measure efficacy from change in \( \log_{10} \) CFU per thigh or lung at the end of 24 hours of therapy
- Correlate efficacy with various pharmacodynamic parameters (Time above MIC, peak/MIC, 24-Hr AUC/MIC)

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000
Relationship Between Peak/MIC Ratio and Efficacy for **Cefotaxime** against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)

No correlation with peak / MIC ratio !!

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig *)

No correlation with AUC / MIC ratio!!

* *2d ISAP Educational Workshop, Stockholm, Sweden, 2000*
Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model (after W.A. Craig * )

![Graph showing relationship between time above MIC and bacterial growth and killing](image)

- Excellent correlation with time above MIC !!

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
End-points of animal models

- Bacterial counts
  - static dose
  - 50% effect
  - $E_{\text{max}}$

- Mortality

- Recovery of resistant bacteria

* 2d ISAP Educational Workshop, Stockholm, Sweden, 2000
Demonstrated advantages of animal models

- Is the magnitude of the parameter required for efficacy the same in different animal species?  
  YES

- Does the magnitude of the parameter vary with:
  1. the dosing regimen?  NO
  2. different drugs within the same class?  NO
  3. different organisms?  Minimal
  4. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)?  NO, but ...

Adapted from W.A. Craig, 2d ISAP Educational Workshop, 2000
PK/PD of fluoroquinolones in clinics

Demonstration of the role of the 24h-AUC / MIC ratio in nosocomial pneumonia

Forrest et al., AAC, 1993

% of patients with positive culture

Days

< 125

125 - 250

> 250
Link between 24h-AUC /MIC and clinical success ...

F. O. Ajayi, ISAP-FDA Workshop, 1999
**24h AUC / MIC : what were the data of the Forrest et al's study ?**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. Pat.</th>
<th>% CureMicrob.</th>
<th>% CureClinical</th>
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<tr>
<td>MIC (mg/L)</td>
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<tr>
<td>&lt;0.125</td>
<td>28</td>
<td>82</td>
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<tr>
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</tr>
</tbody>
</table>

Forrest et al., AAC, 1993
AUC/CMI = 125 : a magical number??

125 was the limit below which failure rates became unacceptable based either:
- on a large MIC
- or on a low dosage
  (AUC is proportional to the dosage)
Is 125 good for all ??

For *S. pneumoniae*, it all depends on your immune status…

For non-neutropenic mice, $E_{\text{max}}$ at 30 ...

For neutropenic mice, $E_{\text{max}}$ at 125 ...

For *S. pneumoniae*, it all depends on your immune status…
Why are the conclusions of the clinical trials apparently (sometimes and apparently) contradictory?

- insufficient separation of covariables
  - only one or a few dosage regimens
- not enough true failures
  - Pathologies pas assez sévères
  - study design
- intercurrent variables influencing outcome and not recognized as such
- unsufficient or inappropriate collection of PK data
  - only “peaks” or troughs...

Correct but uncomplete conclusion

No conclusion possible

Conclusions of poor value (shed confusion…).
Population approaches: Doctor or Regulator?

- In clinical therapy, we would like to give optimal dose to each individual patient for the particular disease

  Individualized therapy

- In new drug assessment / development, we would like to know the overall probability for a population of an appropriate response to a given drug and proposed regimen

  Population-based recommendations

H. Sun, ISAP-FDA Workshop, 1999
Obtaining population cumulative frequencies

Quantal drug concentration effects

Quantal T>MIC plots

H. Sun, ISAP-FDA Workshop, 1999
“Monte Carlo” simulations
Monte Carlo Simulation : the basics …

– “randomly” generating at least 10,000 scenarios of PK and PD parameters that could be seen in patients
– Determining what the PK/PD values would be under each of the 10,000 scenarios
– Forming a histogram of those results. This represents a discrete approximation for the probability distribution of the data.

➢ Monte Carlo simulation allows us to make use of prior knowledge of how a target population handles a specific drug to predict how well that drug will perform clinically at the dose chosen for clinical trials
Monte Carlo Simulation …

*How is this done?*

- Through use of data from a population PK study, a sampling distribution is set up

  ![Image](https://via.placeholder.com/150)

  *think of every body in the world in a bucket from which you randomly select a large number of subjects, each of whom knows their PK parameter values.*

- This allows the pertinent PK parameters to be calculated for all the subjects

- you then only need to apply your pertinent PD parameter!!

*Modified from:*

G. Drusano, Joint ISAP/ECCMID Symposium, Glasgow, UK, May 11th, 2003
“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

1. Patients' PK distribution

2. Bacteria MIC distribution
“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

3. Simulated AUC/ MIC distribution
“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

1. patients

2. broth

3. Simulation …

4. Solve the equations for the AUC values of 3 quinolones …

AUC / MIC

Cipro  Levo  Moxi

0  50  100  200  300
“Monte Carlo” simulation for pneumococci (based on AUC/MIC)

The results are obvious …
Another look at Monte-Carlo simulations: Levofloxacin Vs S. pneumoniae

Certainty is only 80% to get values of AUC:MIC ratio higher than 30.


Those methods allow to know that for each antibiotic:

**PK**
- $C_{\text{max}}$
- AUC
- half-life

**Dosing**

**PD**
- dose response
- Time
- $E_{\text{max}}$

**Therapeutic effects**

**Toxic effects**
Those methods allow to know that for each antibiotic.

**PK**
- $C_{\text{max}}$
- AUC
- half-life

**PD**
- dose response
- Time
- $E_{\text{max}}$

**Dosing**

We now will tell you what these methods show ….

Section 3 c