Can pk/pd replace clinical trials?

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# The Traditional Approach

<table>
<thead>
<tr>
<th>Phase</th>
<th>Participants</th>
<th>Research questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10-50</td>
<td>Tolerability&lt;br&gt;Pharmacokinetics&lt;br&gt;Pharmacodynamics</td>
</tr>
<tr>
<td></td>
<td>Usually young, healthy, male volunteers</td>
<td>Effectiveness&lt;br&gt;Dosage, Safety, PoC</td>
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<tr>
<td>II</td>
<td>100-300</td>
<td>Patients rather than volunteers</td>
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<tr>
<td></td>
<td>1,000 -3,000</td>
<td>Approximate real-life patient population</td>
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<tr>
<td>III</td>
<td>1,000 -3,000</td>
<td>Compare to placebo, current treatments&lt;br&gt;Effects of compound on targets, side-effects</td>
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</tbody>
</table>
Why do we do clinical trials?

• Efficacy (evidence based)
• Safety

Interaction between receptor and ligand

BUT......
Antibiotics? Do they affect us, humans?

Do not know...
Does not feel like it...
Why?
Antimicrobials are supposed to act on microbes

Let's get the suckers!
PK/PD Background
Lowest concentration with no visible growth after 18 hour incubation.

MIC = 2 mg/L

PK

MIC = 2 mg/L
Thus, we have to:
- Establish a relationship between the MIC in vitro and concentrations in vivo (dosing regimens)
- Determine which dosing regimens are optimal in relation to the MIC
AUC and Dose are usually linearly related.
Relationship AUC and effect

- Mice are treated with different dosing regimens
- The number of cfu after 24 is determined/mouse
- AUC for every dosing regimen determined
The figure shows the relationship between Log$_{10}$ CFU/Thigh at 24 Hrs and 24-Hr AUC/MIC, Peak/MIC, and Time Above MIC for levofloxacin and ceftazidim. The data points are plotted for each antibiotic, with levofloxacin on the left and ceftazidim on the right. The graphs indicate the effectiveness of each antibiotic in maintaining concentrations above the MIC for an extended period, which is crucial for bacterial eradication.

Andes IJAA 2002
Fluconazole Pharmacodynamics Against Isogenic Strain Pairs of Susceptible and Resistant C. albicans

Now, what is the Effect of the mic in relation to the dose (or AUC)?
'Normalizing pk/pd relationships'

Pharmacokinetic parameter

concentration

activity

Pharmacodynamic index
Fluconazole Pharmacodynamics Against Isogenic Strain Pairs of Susceptible and Resistant C. albicans

Change in Log10 CFU/Kidneys

24-h Total Dose

24-hr AUC/MIC

R² = 84%

Andes et al ISHAM 2003
Literature Review for T>MIC for Beta-Lactams Versus Mortality in Animal Models

- At least 48 hours of treatment
- Mortality 80-100% in untreated controls
- Pharmacokinetics provided to calculate magnitude of PK/PD parameter
- Mortality recorded within 24 hrs after last dose of drug
- Data from 3 animal species and 4 sites of infection

Craig CID 26:1, 1998; Nicolau et al. AAC 44:1291, 2000
In animals, this has been well established, but is there any clinical evidence?
Comparison of Relationships Between 24-Hr AUC/MIC and Efficacy against Pneumococci for Fluoroquinolones in Animals and Patients

- 58 patients, levofloxacin vs gatifloxacin
- Free-drug 24-hr AUC/MIC <33.7 h, the probability of a microbiologic cure was 64%
- Free-drug 24-hr AUC/MIC >33.7 h, the probability of a microbiologic cure was 100%

Ambrose et al, AAC 45:2793, 2001
Ambrose, AAC 2001
• Relationship between fAUC:MIC ratio & microbiological response from a total 121 patients with respiratory tract infection involving *S. pneumoniae*.

• fAUC:MIC > 34 had 92.6% response rate.

• fAUC:MIC < 34 had 66.7% response rate.
Relationship Between T>MIC and Bacterial Eradication with Beta-Lactams in Otitis Media (Circles) and Maxillary Sinusitis (Squares)

- Animal experiments suggest 40% T>MIC is needed
- Bacteriologic cure for different β-lactams with *S. pneumoniae* and *H. influenzae* from double tap studies in acute otitis media and acute maxillary sinusitis
- Time above MIC calculated from serum levels and MICs for different organisms

IS THIS A SURPRISE?

NO

Because antimicrobials act on microbes, and the exposure relationships in mice are the same as in men.
Use of PK/PD to guide therapy choices

- Aim for an PDI in every patient that will result in a maximum effect
  - Dosing regimen
  - MIC

![Graph showing log (auc) levofloxacin vs. cfu with Max effect at 8 cfu]
Let us answer three questions with respect to antimicrobials:

- Why do we do phase 1 studies?
- Why do we do phase 2 studies?
- Why do we do phase 3 studies?
Phase 1

- Basic clinical pharmacology: biochemistry, pk
- Biological effects
- 10 to 50 healthy volunteers
- First information on the safety, tolerance, and efficacy

- Pharmacokinetic profile in humans
- Single and multiple dosing
- Population pharmacokinetic modelling
- Estimates of dispersion

- Use pk/pd information from animal studies and ivpm
- Monte Carlo Simulations
- Wild Type MIC distribution

Dose selection

Optimal dose for Phase 2
Pharmacokinetics

Some people are more equal than others...
Based on data from Mouton et al, 2002
## Attainment rates of BAL9141

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<th>mic mg/l</th>
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<th>40</th>
<th>50</th>
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**S. aureus ox S (n=50)**  
**S. aureus ox R (n=96)**  

|  |  | 0.25-2 mg/L |  | 0.12-2 mg/L |
|-----------|-----------|----------------|----------------|
| 250 mg q12h | 750 mg q12h |  |  |  |

Mouton et al, ICAAC 2002, AAC 2004
Susceptible (S)

A micro-organism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.

Intermediate (I)

A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indeterminate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

Note: This breakpoints may be altered with legitimate changes in circumstances.

Resistant (R)

Bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances.
A historical mistake

- AUC of a 500 mg levofloxacin dose is appr. 40 mg.h/l
- We wish to have all patients to have an AUC/MIC ratio of > 30-40
- Micro-organisms that have MICs up to appr 1 mg/l should respond well to treatment
With current knowledge, 500 mg qd should not have been approved.
**Phase 2**

- Efficacy
- Pk in patients
- develop pop pk model
- Proof of concept

Establish PI - response Relationship

PI from Pop pk

Response:

- Microbiological cure
- Time to event analysis
- Clinical cure??
3rd phase

2nd phase pk/pd

1st phase pk, escalating D

Lead Optimization

Proof of concept

DR choice

Candidate choice

Allometric scaling

WT distribution

Pharmacokinetics

MIC

Effective value Pharmacodynamic index
What? You really want to test you are efficaceous? With only 700 patients??
Current state of the art 3rd phase...(2)

We laugh at you...
the comparator does not work either......
If 3rd phase studies are performed at all, it should be realized that:

- Antimicrobials kill microbes and do NOT cure patients by themselves. This is not to say that patient cure is not the ultimate goal, but that the endpoint should be microbiological rather than clinical.

- If possible, a continuous rather than a dichotomous variable for efficacy should be chosen to increase the power of the study.
Baseline = control
Max effect = observed
Dose - AUC relationship

Mouton et al 1999
Why do we do clinical trials?

• **Efficacy** (evidence based)

• **Safety**

![Conc/dose. vs effect](Image)

Interaction between receptor and ligand

**BUT**......
Pharmacokinetics/Pharmacodynamics Applied in All Stages of Antiinfective Research

**Phase 1**
- Basic clinical pharmacology: biochemistry, pk
- Biological effects
- 10 to 100 healthy volunteers
- First information on the safety, tolerance, and efficacy

**Phase 2**
- Dose finding
- pk
- Efficacy

**Phase 3**
- Efficacy?
- Toxicity?
- pk?

**Phase 4**
- Toxicity, AE
- Indications+
What Makes Clinical Trials Ethical?

• Social or scientific value
• Scientific validity & independent review
• Favorable risk-benefit ratio
• Fair subject selection
• Informed consent
• Respect for potential and enrolled subjects

Emanuel, Ezekiel, et. al. “What Makes Clinical Research Ethical?”
This contribution could not have been possible without the input of
<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Objective of Study</th>
<th>Study Examples</th>
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| Human Pharmacology | • Assess tolerance  
• Define/describe PK\(^1\) and PD\(^2\)  
• Explore drug metabolism and drug interactions  
• Estimate activity | • Dose-tolerance studies  
• Single and multiple dose PK and/or PD studies  
• Drug interaction studies |
| Therapeutic        | • Explore use for the targeted indication  
• Estimate dosage for subsequent studies  
• Provide basis for confirmatory study design, endpoints, methodologies | • Earliest trials of relatively short duration in well-defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures  
• Dose-response exploration studies |
| Exploratory        |                                                                                                              |                                                                                                     |
| Therapeutic        | • Demonstrate/confirm efficacy  
• Establish safety profile  
• Provide an adequate basis for assessing the benefit/risk relationship to support licensing  
• Establish dose-response relationship | • Adequate, and well controlled studies to establish efficacy  
• Randomised parallel dose-response studies  
• Clinical safety studies  
• Studies of mortality/morbidity outcomes  
• Large simple trials  
• Comparative studies |
| Confirmatory       |                                                                                                              |                                                                                                     |
| Therapeutic Use    | • Refine understanding of benefit/risk relationship in general or special populations and/or environments  
• Identify less common adverse reactions  
• Refine dosing recommendation | • Comparative effectiveness studies  
• Studies of mortality/morbidity outcomes  
• Studies of additional endpoints  
• Large simple trials  
• Pharmacoeconomic studies |
|                    |                                                                                                              |                                                                                                     |