Current Tools and Approaches for setting (clinical) Breakpoints

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Professor pharmacokinetics and pharmacodynamics
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 breakpoint 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.
LAB REPORT

• Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)
• Distinguish, based on in vitro test results, patients with high likelihood of cure from those with a low(er) likelihood.

• We use the terms susceptible and resistant as class markers

• Thereby help the clinician in informed decision making

• Are not absolute, but provide a means to the former
  • Is therefore dependent on risk versus benefit

• Are dependent on dose / exposure
Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products
4. MAIN GUIDELINE TEXT

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SETTING A BREAKPOINT
(the easy approach)

DETERMINE DOSE-RESPONSE RELATIONSHIP

DETERMINE BREAKPOINT (dose-dependent)
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

Treatment with fluconazol
Doses 50 – 800 mg

Culture-results with
MIC-values

Individual Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)

Clinical outcome

Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

Treatment with fluconazol
Doses 50 – 800 mg

Culture-results with
MIC-values

Individual Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)

Clinical outcome
Probability of cure after treatment with fluconazole
Oropharyngeal Candidiasis n=132

- Prob cure correlates with Dose/MIC
- POSITIVE correlation with Dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain Dose/MIC value

Rodriguez- Tudela et al, AAC 2007
Usually however, it is slightly more complicated than just dose........

Dose is just a **means** to reach adequate (effective) concentrations / concentration profiles.
Usually however, it is slightly more complicated than just dose........

......because in development we usually do not have Dose – response relationships

......we need to know how to dose adjust, if required, based on patient-specific characteristics
Usually however, it is slightly more complicated than just dose.

Dose is just a **means** to reach adequate (effective) concentrations / concentration profiles

Establish Exposure-Response Relationships
Unravelling the relationship between dose and response

ACTIVITY
in vitro (MIC)

CONCENTRATIONS
in vivo (PK)

DOSING regimen

ANTIMICROBIAL EFFICACY
(Microbiological Cure)

Other factors

CLINICAL EFFICACY
(Clinical Cure)
Usually however, it is slightly more complicated than just dose........

Dose is just a **means** to reach adequate (effective) concentrations/concentration profiles

Establish Exposure-Response Relationships
Usually however, it is slightly more complicated than just dose.

Dose is just a **means** to reach adequate (effective) concentrations / concentration profiles.

- Optimal exposure
- Pharmacodynamic target
- Establish Exposure-Response Relationships
Pharmacodynamic Target

The exposure required for the desired effect
SETTING A BREAKPOINT

1. Determine dose-response relationship

2. Determine breakpoint (dose dependent)

3. Determine the PK/PD target
   - e.g. value of the PK/PD index
     (animal studies, clinical studies)

4. Estimate exposure
   - from the dosing regimen and PK, including population variability

5. Determine PK/PD breakpoint
   - from $PK/PD\ target = PK/PD\ Index$
SETTING A BREAKPOINT

DETERMINE THE PK/PD TARGET  e.g. value of the PK/PD Index
(Animal studies, clinical studies)

ESTIMATE EXPOSURE  from the dosing regimen and PK, including population variability

DETERMINE PK/PD BREAKPOINT  from PK/PD target = PK/PD Index
Pharmacokinetic parameters: Measures of Exposure

- **PEAK**
- **AUC**
- **T > MIC**
- **MIC**
Any idea where we are today?

No idea… may be a mouse?

 Might be a human, though…
A clear relationship exists between exposure and effect.

A maximum effect is reached at ratio's of 25-35 (mortality).

- The pharmacodynamic target

Each data point represents the proportion of mice cured within a group representing a certain AUC/MIC value.
Relationship between fAUC/MIC and Effect
121 patients with S. pneumoniae respiratory infection

fAUC/MIC cut-off ~34

- 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.
Pharmacodynamic targets

• Animal models
• In vitro models (Hollow fiber)
• Time kill curves and modelling

The Target should Reflect the Indication
SETTING A BREAKPOINT

DETERMINE THE PK/PD TARGET    e.g. value of the PK/PD Index
(animal studies, clinical studies)

ESTIMATE EXPOSURE  from the dosing regimen and PK, including population variability

DETERMINE PK/PD BREAKPOINT  from PK/PD target = PK/PD Index
Pharmacokinetics

Some people are more equal than others…
fAUC distribution levofloxacin
(monte carlo simulation)
fAUC distribution levofloxacin
(monte carlo simulation)
Slide withheld at request of author
PTA of ceftazidime, volunteers
1000 mg q8h

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>%T &gt; MIC 30</th>
<th>%T &gt; MIC 40</th>
<th>%T &gt; MIC 50</th>
<th>%T &gt; MIC 60</th>
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<td>100% PTA</td>
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Population modelling and Monte Carlo simulations

- **Purpose of population modelling**
  - Try to capture all variation as much as possible in a set of pharmacokinetic parameters
  - Explain and predict concentrations in individual patients
    - Sparse sampling
    - Co-variates

- **Purpose of MCS (using a population model) in breakpoint setting**
  - Try to predict the future using parameter estimates and its variation to capture the variation in the population to be treated – and derive the clinical breakpoint
Purpose of population modelling and monte carlo simulations

• **Purpose of population modelling**
  • Try to capture all variation as much as possible in a set of parameters
  • Predict concentrations in individual patients
    • Sparse sampling
    • Co-variates

• **Purpose of MCS in breakpoint setting**
  • try to predict the future using poppk parameter estimates and its variation to capture the variation in the population to be treated

Problem: MCS is used using POPPK developed for another purpose And therefore ‘true’ variation may be underestimated
Specific issues

1. Different populations will yield different models
   - Parameter estimates
   - Variation

2. Different simulations
Different Models.....different simulations
ceftazidime

Volunteers

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>30</th>
<th>40</th>
<th>50</th>
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<tr>
<td>100% PTA</td>
<td>8</td>
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CF patients

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<th>50</th>
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ICU patients

<table>
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<tr>
<th>MIC (mg/L)</th>
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<th>60</th>
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<td>32</td>
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<td>32</td>
<td>27</td>
<td>23</td>
</tr>
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Mouton et al, Clin Ther 2005 27:762

JWM Vienna 21-09-2016
Specific issues

1. The variation present in the population will determine the outcome of the MCS

2. More variation: wider confidence interval

Which range of covariables to include to build the model? Or sims with different covariate values?

- 50-150 crcl? Or 20-200? Or 80-120?
- 50-100 kg? Or 120?
- Older patients? Younger patients?

*Should represent the population to be treated*
POP PK model of POL7080 including covariates

Table 1. Characteristics of the study-population of 52 volunteers and 21 patients with renal impairment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>30.4</td>
<td>18-77</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1</td>
<td>56.4-108.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.0</td>
<td>19.6-34.9</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>103.2</td>
<td>19-161.0</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>8/11</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Estimates of the final population PK model. The final model consisted of 3 compartments, variability on CL, V1, V2 and V3 and 4 covariates: creatinine clearance on the clearance of POL7080, weight on V1, and age on V2 as well as on V3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>Relative SE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>θ1: Clearance (liter/h)</td>
<td>5.62</td>
<td>0.139</td>
<td>2.47</td>
</tr>
<tr>
<td>θ2: Volume of distribution 1</td>
<td>0.82</td>
<td>0.487</td>
<td>5.52</td>
</tr>
<tr>
<td>θ3: Volume of distribution 2</td>
<td>18.8</td>
<td>0.855</td>
<td>4.33</td>
</tr>
<tr>
<td>θ4: Volume of distribution 3</td>
<td>8.31</td>
<td>0.518</td>
<td>6.23</td>
</tr>
<tr>
<td>θ5: Intercompartmental clearance</td>
<td>2.06</td>
<td>0.184</td>
<td>8.90</td>
</tr>
<tr>
<td>θ6: Intercompartmental clearance</td>
<td>7.86</td>
<td>0.961</td>
<td>12.5</td>
</tr>
<tr>
<td>θ7: Covariate creatinine clearance on CL</td>
<td>0.00758</td>
<td>2.306×10^-4</td>
<td>3.14</td>
</tr>
<tr>
<td>θ8: Covariate weight on V1</td>
<td>0.0183</td>
<td>0.00149</td>
<td>8.18</td>
</tr>
<tr>
<td>θ9: Covariate age on V2</td>
<td>0.0173</td>
<td>0.00023</td>
<td>135.4</td>
</tr>
<tr>
<td>θ10: Covariate age on V3</td>
<td>0.0145</td>
<td>0.00245</td>
<td>16.9</td>
</tr>
<tr>
<td>θ11: Variability on clearance</td>
<td>0.0357</td>
<td>0.00748</td>
<td>22.4</td>
</tr>
<tr>
<td>θ12: Variability on V1</td>
<td>0.0752</td>
<td>0.00246</td>
<td>32.3</td>
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<tr>
<td>θ13: Variability on V2</td>
<td>0.0398</td>
<td>0.00153</td>
<td>5.08</td>
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<tr>
<td>θ14: Variability on V3</td>
<td>0.0234</td>
<td>0.00681</td>
<td>29.1</td>
</tr>
</tbody>
</table>

Figure 1. Relationship between covariate and parameter estimate in the model as well as the equations.
PTA for different creatinin clearances

Model with covariates
Relation between Creatinin Clearance and Meropenem Clearance
In 238 Criticall Ill Patients on 557 occacions during Continuous Infusion

Regression=
Not significant

No model assumptions
Specific issues

• Should covariates be build in the model when simulating?
  • Purpose of MCS is *not* knowing the covariate values!!

• More variation : wider confidence interval
Slide withheld at request of author
• **Purpose of population modelling**
  • Try to capture all variation as much as possible in a set of parameters
  • Predict concentrations in individual patients
    • Sparse sampling
    • Co-variates

• **Purpose of MCS in breakpoint setting**
  • try to predict the future using parameter estimates and its variation to capture the variation in the population to be treated

• **What is acceptable without over- or underestimating?**
What do we need after modelling?

Judgement, informed decision making
What do we need after modelling?

- **Judgement is a human task taking into account all the information available and weighing the risks and benefits**
  - Dosing regimens: efficacy, toxicity
  - How much predicted failure is accepted? 1, 5, 10%?
  - How can risks be minimized by finetuning methods and assumptions?
  - How can variation in the population be captured in the PTA

- **Every simulation is just a part of a chain – decision making is an iterative process. If new information becomes available, it should be used.**
What do we need during development?

- **Based on pkpd, determine optimal dosing based on the clinical indication and micro-organisms expected using the iterative process**

- **Determine the risks and benefits of specific circumstances and patients**

- **Optimal dosing will provide the clinical breakpoint**

- **In the end during and after, determine the factors that allow individualized (personalized) treatment**
The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

Preclinical PK/PD studies

- Correlation exposure–effect

Clinical PK/PD studies

- Correlation exposure - effect

PD target

Qualitative relationship (PK/PD index)

PD target

Qualitative relationship (value PK/PD index)

Clinical dosing regimen

Monte Carlo simulations

Initial PK/PD breakpoint

MCS robustness target population dose adjustments

PK/PD breakpoint

MIC distributions

**FIG. 7.** Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.
Conclusions

- PKPD is useful to define clinical breakpoints but consider:
  - The variation in pharmacodynamic targets
  - The population of interest should reflect the population modelled
  - The inclusion of covariates should be considered carefully

- It would be more useful to determine the PTA for different values and combinations of covariates (in particular renal clearance) to draw overall conclusions instead of just one model

- Acceptable PTAs are relative

- Clinical breakpoints do not cover all eventualities but provide general recommendations. Dose adjustment is always required by the clinician in specific circumstances to compensate for exceptional circumstances (covariate values).