Pharmacodynamics: the concepts

• What is pharmacodynamics?
• Dose-response models
  – The yes/no model
  – The linear model
  – The sigmoidal model
• Influence of time

With the support of Wallonie-Bruxelles-International
What is pharmacodynamics?

what the drug does to the body ...

**Pharmacodynamics**
conc vs effect

Effect

Conc (log)
Pharmacokinetics

Pharmacodynamics

Dosage

Serum concentration varying over time

Concentration at the site of infection → Therapeutic effects

Concentration in non-target tissues → Toxic effects
**Pharmacodynamics**

- Concentration at the site of infection → **Therapeutic effects**
- Concentration in non-target tissues → **Toxic effects**

**Pharmacokinetics**

- Dosage → Serum concentration varying over time

- **Dosage**
Pharmacodynamics: the yes and no model ....

- sharp threshold
- maximal effect immediately observed

This is the model assumed by
- the breakpoints approach !! (S - R)
- the cured / non-cured clinical endpoint !!
Pharmacodynamics: the linear model...

- continuously increasing effect
- effect matches dosing

This is the model assumed by the "high dosing in severe infections" approach ...

→ the more you give, the more it must be active... No?
Pharmacodynamics: the sigmoidal dose-response model

- starting threshold
- dose-response in a given zone
- maximum reached

This is the classical pharmacological model and corresponds to reality.
Pharmacodynamics: the sigmoidal dose-response model

lowest limit of action
Pharmacodynamics: the sigmoidal dose-response model

This is where increasing the dose is useful

Lowest limit of action
Pharmacodynamics: the sigmoidal dose-response model

- **Lowest limit of action**: This is where increasing the dose is useful.
- **Maximal effect**: This is where you get your maximal effect.
Sigmoidal response: the importance of the shape of the curve

The "shape factor" describes the steepness of the response ...
Some antibiotics are steep, others are less steep...

β-lactams, vancomycin, …
- narrow dose-response zone
- tendency to yes/no

aminoglycosides, fluoroquinolones
- wide dose-response zone
- increasing the concentration causes more effect
Pharmacodynamics: influence of time...

All antibiotics are dependent on time...

![Graph showing the killing effect of antibiotics on bacterial growth over time](image)
Pharmacodynamics: influence of time...

But some kill so fast that time becomes unimportant.

With an aminoglycoside (tobramycin), or a fluoroquinolone (ciprofloxacin) a 4 log decrease is achieved in less than 4-6 h at 4 X the MIC.
Pharmacodynamics: influence of time ...

But some kill so fast that time becomes unimportant.

But with a β-lactam, you achieve only a 2 log decrease in 6 h,

... and it does not go much faster if you increase the concentration above 4 X the MIC.
### Pharmacodynamics: concentration x time

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose Response</th>
<th>Influence of Time</th>
<th>Clinical Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-lactams (all)</td>
<td></td>
<td>Narrow</td>
<td>Expose must be prolonged</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolides</td>
<td></td>
<td>Critical</td>
<td>High concentrations are unimportant</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Large</td>
<td>Limited</td>
<td>Concentrations are important</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td>Time is not critical</td>
</tr>
</tbody>
</table>

- Exposure must be prolonged
- High concentrations are unimportant
- Concentrations are important
- Time is not critical
Some antibiotics are less powerful than others: look for $E_{\text{max}}$

Poorly bactericidal:
- vancomycin
- macrolides
- tetracyclines
But some antibiotics are more powerful than others
Some antibiotics are more powerful than others: look for $E_{\text{max}}$

Highly bactericidal:
- fluoroquinolones
- aminoglycosides
E max tells you how active you are …

- **Highly bactericidal**
  - fluoroquinolones
  - aminoglycosides

- **Poorly bactericidal**
  - vancomycin
  - macrolides
  - tetracyclines

Graph showing absolute antibacterial effect (killing in arbitrary units) vs. log C ng/ml.
This is where we are now ...

**Dosing**

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

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

**Therapeutic effects**

**Toxic effects**
This where we are now ...

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

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

Dosing

Therapeutic effects

Toxic effects

We will now see the methods used ...

Section 3  b