Pharmacokinetics and Pharmacodynamics for antimicrobial medicines

The module has been written by
Tim Hills MRPharmS, DipClin
Lead Pharmacist Antimicrobials and Infection Control
Nottingham University Hospitals NHS Trust

This learning module is intended for UK healthcare professionals only.
I. Introduction
II. Drug factors in treatment of infections
III. Main indices of antimicrobial efficacy
IV. Evaluation
Introduction
Aim of the course

To provide healthcare professionals with an understanding basic pharmacokinetic principles and PK/PD indices applied to antimicrobial treatment.
Upon completion of this module, participants will be able to:

- Describe what pharmacokinetics and pharmacodynamics mean and the importance of PK/PD indices to drug dosing.

- Recognise the 3 most common PK/PD indices and assign them to common groups of antimicrobials.

- Evaluate potential drug dosing regimens applying knowledge of their PK/PD index.
Drug factors in treatment of infections
Treatment of infection

Treatment success depends on a number of factors:

- **Host factors**
  - Immunity
  - Comorbidities
  - Perfusion to infection site
  - Drug handling

- **Drug factors**
  - Hydrophilicity
  - Protein binding
  - Molecular weight
  - Affinity with antimicrobial target

- **Bug factors**
  - Minimum inhibitory concentration

- **Infection factors**
  - Biofilm
  - Site of Infection
  - Pathogen density
Pharmacokinetics (PK) is how the body “handles” the drug, how a drug is absorbed distributed and eliminated from the body. It depends on both Drug and Host factors.
The four processes involved when a drug is taken are absorption, distribution, metabolism and elimination or excretion (ADME).

- Absorption
- Distribution inc. Volume of distribution
- Metabolism and Excretion
- Clearance
Definitions of basic ADME Concepts

Absorption

• Absorption is the movement of a drug from its site of administration into the blood. Absorption is affected by blood flow, pain stress, method of administration (oral or parenteral, size of a drug molecule etc).

• Bioavailability is the proportion of the dose which remains active once it is in the general circulation.

• For intravenous dosing this is 100% but for oral dosing bioavailability is more relevant. Antibiotics with high oral bioavailability are good candidates for prompt IV to PO switch.
Definitions of basic ADME Concepts – cont.

- **Distribution** describes where the drug moves throughout the body and in what proportions.

- For example, to treat meningitis we require an antibiotic which readily crosses an inflamed blood-brain barrier.

- Drugs can distribute and bind to **plasma proteins**. Only the free-drug can enter a microorganism but the protein-bound drug can act as a reservoir.
The apparent **Volume of Distribution (Vd)** is a theoretical concept. It describes the volume of plasma that would be necessary to account for the total amount of drug in the patient's body, if that drug were present throughout the body at the same concentration as found in the plasma. It is used when trying to estimate the dose of drug required to obtain a desired plasma concentration.

For example, a 50kg patient was given 1000mg of Drug A. After allowing for drug distribution a blood sample is analysed to show a concentration 10mg/L free-drug. The apparent volume of distribution in this patient is 100 litres or 2L/kg as this is the volume required to dilute the total dose to a 10mg/L concentration.

For further explanation see: [http://www.nottingham.ac.uk/nmp/sonet/rlos/bioproc/vd/2.html](http://www.nottingham.ac.uk/nmp/sonet/rlos/bioproc/vd/2.html)
Basic ADME Concepts –cont.

• **Metabolism** is when the body chemically alters the drug, usually to make it more water soluble and easier to excrete.

• **Excretion** is when it a drug is removed from the body.

• **Clearance** describes the rate of removal of active drug through metabolism and/or excretion.
When a drug is administered it is initially absorbed and distributed and then cleared from the body.
Definition of Pharmacodynamics

• Pharmacodynamics (PD) is the study how a drug acts on the body, or in the case of an antimicrobial, a microorganism. It depends on both **Drug and Infection** factors.

- **Drug factors**
  - Hydrophilicity
  - Protein binding
  - Molecular weight
  - Affinity with antimicrobial target

- **Host factors**
  - Immunity
  - Comorbidities
  - Perfusion to infection site
  - Drug handling

- **Bug factors**
  - Minimum inhibitory concentration

- **Infection factors**
  - Biofilm
  - Site of Infection
  - Pathogen density

- **Treatment success**
Pharmacodynamic concepts

Minimum Inhibitory Concentration.

• This is the lowest concentration of antimicrobial required to stop the growth of the micro-organism.
Biofilms – these are communities of micro-organisms which encase themselves in extracellular secretions. As antimicrobials have to pass through the secretions to get to the micro-organisms higher concentrations are required to kill them. Biofilms can form on any areas but are particularly common on prosthetic material.
Main indices of antimicrobial efficacy
Pharmacokinetics/Pharmacodynamics (PK/PD) combines these two sets of parameters.

The results is a specific drug-concentration profile target which can be varied with bacterial MIC.

- There are three main indices relevant to antimicrobial efficacy.
  - Time above the MIC (T>MIC)
  - Peak concentration divided by the MIC (C_{max}/MIC)
  - Area under the curve divided by the MIC (AUC/MIC)
For some drugs such as aminoglycosides it is the **height of the peak** which is most important. These drugs have a significant post-antibiotic effect where growth continues to be inhibited despite the concentration dropping below the MIC. Traditionally, aminoglycosides were administered as multiple daily dosing regimens. These days drugs are often given as a single daily dose to maximize the efficacy whilst reducing toxicity. **Cmax/MIC is sometimes termed “concentration dependent” effect.**
With “Time above the MIC” the height of the initial peak is not important, what matters is the % of time where the concentration is above the MIC. Beta-lactams antibiotics such as penicillins have this index. These drugs are sometimes given as prolonged or continuous infusion to improve efficacy in difficult to treat infections. Time above the MIC is sometimes called “time dependent” or “concentration independent” effect.
AUC/MIC

For most antimicrobials both the time and concentration are important which are represented in the index “area under the concentration/time curve divided by the MIC”. AUC is proportional to the total daily dose regardless of how it is administered so must be increased to treat more difficult infections.
Determining PK/PD indices

• PK/PD indices are usually determined using in vitro animal models.

• Different concentrations of antibiotic are introduced against the infection.

• Graphs are plotted between the various indices and efficacy measured as a reduction in the number of viable microorganisms.

• Regression analysis is used to determine the closest relationship.
This table summarises the indices relating to major antimicrobials

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Index in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Cmax/MIC ≥ 8-10</td>
</tr>
<tr>
<td>Beta-lactams: Cephalsporins</td>
<td>T&gt;MIC 40-70% Critically ill patients 100%</td>
</tr>
<tr>
<td>Penicillins</td>
<td></td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>AUC/MIC and T&gt;MIC</td>
</tr>
<tr>
<td>Glycopeptides</td>
<td>AUC/MIC &gt;400</td>
</tr>
<tr>
<td>Quinolones</td>
<td>AUC/MIC ~125 vs Gram Positive organisms 40 Vs Gram negative</td>
</tr>
<tr>
<td></td>
<td>Some concentration dependent effects</td>
</tr>
<tr>
<td>Azoles</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Lipopeptides</td>
<td>AUC/MIC and Cmax/MIC</td>
</tr>
</tbody>
</table>
PK/PD indices

The index chosen is specific to the drug whereas bug factors are accounted for by the MIC of the organism.

The PK/PD targets relate to the free-drug plasma concentration. So they still need to be considered in the context of the Infection and Host factors. For example the concentration of drug within the CSF is often significantly lower than that of the serum so higher doses are often required.

The index, MIC and distribution can be combined to design an appropriate dosing regimen.
Your patient has a bloodstream infection and you have been asked to calculate what dose of Antibiotic A should be prescribed.

- PK/PD index for Antibiotic A: Cmax of ≥10 x MIC.
- Patient weight: 60kg
- Bacterial MIC: 2mg/L
- Volume of distribution for Antibiotic A: 0.25L/kg

The PK/PD index for Antibiotic A is a Cmax of 10 x the MIC.
A 60kg patient has a bloodstream infection, the bacteria has an MIC of 2mg/L.
So the target plasma free-drug target concentration is 10 x 2mg/L = 20mg/L.
The volume of distribution for Antibiotic A is 0.25L/kg or 0.25L/kg x 60kg = 15L for this patient.
So the dose to prescribe is 15L x 20mg/L = 300mg.
References

Nynke GL et al Therapeutic drug monitoring of anti-infective agents in critically ill patients
http://dx.doi.org/10.1586/17512433.2016.1172209
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Evaluation
QUESTION 1

WHICH OF THE FOLLOWING IS NOT A FACTOR OF ANTIBIOTIC TREATMENT SUCCESS

1. Host factors.
2. Bug factors.
3. Drug factors.
4. Infection factors.
5. Air humidity factors.
WHICH OF THE FOLLOWING ARE BASIC CONCEPTS OF PHARMACOKINETICS (Select all that apply)

1. Absorption.
2. Peristalsis.
3. Metabolism and Excretion.
QUESTION 3

WHAT DOES MIC STAND FOR?

1. Maximum inhibitory concentration.
2. Maximum infection coverage.
3. Minimum inhibitory concentration.
4. Minimum infection coverage.
WHICH OF THE FOLLOWING IS NOT A MAIN INDICE RELEVANT TO ANTIMICROBIAL EFFICACY?

1. Time above the MIC.
2. The drug formulation.
3. Peak concentration divided by the MIC (Cmax/MIC).
4. Area under the curve divided by the MIC (AUC/MIC).
WHICH OF THE FACTORS IS ACCOUNTED FOR BY THE MIC OF THE ORGANISMS

1. Host factors.
2. Bug factors.
3. Drug factors.
4. Infection factors.
WHICH OF THE FOLLOWING IS NOT CORRECT REGARDING THE BASIC ADME CONCEPTS MENTIONED

1. Metabolism is when the body chemically alters the drug, usually to make it more water soluble and easier to excrete.
2. Excretion is when a drug passes the blood-brain barrier.
3. Clearance describes the rate of removal of active drug through metabolism and/or excretion.
1. The study of how a drug acts on the body.
2. How the body “handles” the drug through absorption, distribution and elimination.
3. How the drug moves throughout the body and in what proportions.
4. The volume of plasma that is necessary to account for the total amount of drug in the patient’s body, if the drug were present at the same concentration throughout the body.
1. Minimum Inhibitory Concentration is the lowest concentration of antimicrobial required to stop the growth of the micro-organism.

2. Biofilms are micro-organisms which encase themselves in an extracellular secretion.

3. Biofilms are particularly common on prosthetic material.

4. **Lower concentrations of antimicrobials are required to kill biofilms.**
Certificate of completion

Name: ......................................................

Completed training course:
Pharmacokinetics and Pharmacodynamics
for antimicrobial medicines