Antimicrobial Properties
Pharmacokinetics & Pharmacodynamics

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Outline

• Define the terms: pharmacokinetics (PK) and pharmacodynamics (PD)

• Explain the importance of understanding PK & PD properties for antibiotics

• Discuss the pharmacokinetic properties of antibiotics

• Discuss the pharmacodynamic properties of antibiotics
What is Pharmacokinetics?

• Derived from the Ancient Greek:
  – Pharmakon : Drug
  – Kinetikos : to do with motion

• The science of the rate of movement of drugs within biological systems, as affected by the absorption, distribution, metabolism, and elimination of medications.
What is Pharmacodynamics?

The study of the action or effects of drugs on living organisms
Pharmacokinetics refers to what the body does to the drug.

Pharmacodynamics refers to what the drug does to the body.
PK & PD of Antibiotics

Why do we need to know?

Maximum BENEFIT

Minimal SIDE EFFECTS
Case - ICU

75 yo woman was admitted to the ICU and started on the following:

Amikacin 1 gm IV daily
Vancomycin 1 gm IV Q12h
Levofloxacin 750 mg IV daily

On admission, SCr was 1.1 (ClCr 40 ml/min)
On day 4, urine output decreased, SCr increased to 2.7 and continued to worsen.
Vancomycin trough: 55 mg/L (therapeutic range 15-20)
Cont Case - ICU

- **Distribution** of Amikacin is minimal to the adipose tissue; dosing is based on the IBW.

- **Excretion** of Vancomycin and Amikacin is renally; dosing interval should be adjusted in patients with renal impairment.

- **PK & PD variability** among patients; vancomycin and amikacin levels used.

- **Nephrotoxicity** increases when vancomycin and amikacin are combined.
Pharmacokinetics of Antibiotics

- Absorption
- Distribution
- Metabolism
- Excretion
Absorption

• Drug characteristics that affect absorption:
  – Molecular weight, ionization, solubility, & formulation

• Patient factors affecting drug absorption:
  – Route of administration
  – Acidity/Alkalinity of stomach/intestine
  – Rate of gastric emptying
  – Presence of food in the stomach
Absorption

• Rate and extent of absorption is referred to as bioavailability.
• Bioavailability depends on the route of administration.
• IV route has 100% bioavailability.
• Some antibiotics have excellent oral bioavailability >90% (e.g., levofloxacin, ciprofloxacin, fluconazole)
Distribution

- Membrane permeability
  - cross membranes to site of action
- Plasma protein binding
  - malnutrition = ↓albumin = ↑ free drug
  - High protein bound drug has a smaller amount of drug free to act at the receptor site
- Blood flow to tissues
  - Heart, liver, and kidneys - high amount of blood flow
  - Muscle, fat – low amount of blood flow
- Lipophilicity of drug
  - lipophilic drugs accumulate in adipose tissue
Distribution

- Daptomycin does not have adequate distribution to the lungs and should not be used in patients with pneumonia.

- Vancomycin has poor penetration to the lungs; higher doses are required.
Metabolism

- Drugs and toxins are seen as foreign to patients’ bodies

- Drugs can undergo metabolism in the lungs, blood, and liver

- Body works to convert drugs to less active forms and increase water solubility to enhance elimination.

- Liver is the primary site for drug metabolism.
Elimination

- Pulmonary = expired in the air
- Bile = excreted in feces
  - enterohepatic circulation
- Renal
  - glomerular filtration
  - tubular reabsorption
  - tubular secretion
- Most antibiotics are excreted renally and require dose adjustments in patients with renal failure.
Pharmacokinetic Concepts

Half-life of drugs

Half-life = time required for drug concentrations to decrease by one-half (50%)
Pharmacokinetic Concepts
Steady State

- Amount of drug administered is equal to the amount of drug excreted.
- Results in a plateau or constant serum drug level.
Pharmacodynamic Properties

- Concentration-dependent killing:
  - direct relationship between antibiotic concentration and bactericidal effect.

- Time-dependent:
  - maximal suppression of organism is maintained as long as antibiotic concentrations remains above the MIC.

- Postantibiotic effect (PAE):
  - describes persistent suppression of bacterial growth after antimicrobial exposure.
    - PAE: implies that the effect is due to prior exposure rather than persistent inhibitory concentration.
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<tr>
<th>Concentration - dependent killing</th>
<th>Time-dependent killing</th>
<th>PAE Gram+</th>
<th>PAE Gram-</th>
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<tr>
<td>Aminoglycosides</td>
<td>Beta-lactams</td>
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<td>Aminoglycosides</td>
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<tr>
<td>Quinolones</td>
<td>Macrolides</td>
<td>Glycopeptides</td>
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<td>Streptogramins</td>
<td>Macrolides</td>
<td>Carbapenems</td>
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<td>Chloramphenicol</td>
<td>Streptogramins</td>
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Pharmacodynamic Parameters

**Pharmacodynamic Parameters & Outcome**

- $C_{\text{max}} = \text{Peak}$
- $C_{\text{max}} / \text{MIC}$
- $\text{AUC} / \text{MIC}$

**Conc.**

- **Aminoglycosides**
  - Fluoroquinolones
  - Macrolides
  - Ketolides
  - Glycopeptides
  - Lipopeptides

- **Beta-lactams**
  - Tetracycline
  - Oxazolidinones

- $T > \text{MIC}$

- $\text{MIC}$

- $C_{\text{min}} = \text{Trough}$

**Time**

Summary

- Pharmacokinetics (PK): the effect of the body on the drug.
- Pharmacodynamics (PD): the effect of the drug on the body.
- Understanding the PK and PD of antibiotics helps achieve maximum benefit with less side effects.
- Bioavailability: rate and extent of drug absorption; is affected by drug and patient characteristics.
- Distribution of the antibiotics determines whether the antibiotic can be used for a specific infection (e.g., daptomycin, vancomycin)
- Metabolism: liver is the major site of drug metabolism.
- Excretion: the kidneys are the major site of drug excretion.
- Most antibiotics require dose adjustments in renal failure.
Summary

• Pharmacodynamics properties of antibiotics includes:
  – Concentration dependent killing
  – Time dependent killing
  – Post-antibiotic effect

• Dose and dosing frequency of antibiotics are determined based on the PK and PD properties.
Thank You

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