Pharmacodynamics & Pharmacokinetics Made Ridiculously Simple

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PHARMACODYNAMICS & PHARMACOKINETICS

I. Definitions

A. Pharmacodynamics
   • the study of drug action at the biochemical level
     ➔ process by which drugs influence cell physiology
     ➔ “mechanism of action” of a drug

B. Pharmacokinetics
   • the study of how drugs enter the body, reach their site of action, and are eliminated from the body

II. Pharmacodynamics

• there are 2 major types of pharmacologic action:

A. drugs which change the environment of body cells

   • antacids (e.g., Maalox, Mylanta) ➔ neutralize stomach acidity
   • NaHCO₃ ➔ alkalinize urine ➔ change drug excretion rates

B. drugs which bind to receptors on cell membranes and alter cellular physiology

   • digoxin ➔ binds to receptors on myocardial cells
     ➔ increases calcium influx
     ➔ increases myocardial force of contraction

(1) Drug-Receptor Interaction ("Lock-and-Key" Mechanism)

a. agonist ➔ drug which binds to a specific receptor and produces a physiological effect by stimulating the receptor

   • NE (norepinephrine) ➔ stimulates beta-1 receptors on SA node
     ➔ increases heart rate

b. antagonist ➔ drug which binds to a specific receptor and blocks other substances from stimulating the receptor

   • diphenhydramine (Benadryl) ➔ blocks histamine-1 receptors
     ➔ prevents allergic reactions
Drug-Receptor Interaction ("Lock-and-Key" Mechanism)

b. antagonist (cont.)

- propranolol (Inderal) → blocks beta-1 receptors on SA node → decreases heart rate
- naloxone (Narcan) → blocks opiate receptors in respiratory center → reverses respiratory depression due to heroin (narcotic) overdose

(2) Receptor Binding Characteristics

a. affinity: the ability of a drug to bind to its receptor

- agonist → affinity
- antagonist → affinity

b. efficacy: the ability of a drug to stimulate its receptor

- agonist → efficacy
- antagonist → no efficacy

(3) Competitive Inhibition

- occurs when agonist and antagonist compete for occupation at the same receptor site:
  - morphine (agonist) ↔ Narcan (antagonist)
  - Valium (agonist) ↔ Romazicon (antagonist)
  - acetylcholine (agonist) ↔ atropine (antagonist)

III. Pharmacokinetics
(drug absorption → drug distribution → drug metabolism → drug excretion)

A. Drug Absorption (how drugs enter the bloodstream)

(1) routes of administration

a. oral (PO)

- 80% of drugs used in medical practice are given orally
- route is convenient and economical
- drug is ingested → absorbed from the stomach / intestine → enters hepatic portal circulation → liver → enters general circulation
b. sublingual (SL)

- drug is dissolved under the tongue and is absorbed through mucous membranes into the bloodstream
- route is convenient and economical
- example: nitroglycerin (NTG) sublingual tablets

c. transdermal (TD)

- drug (contained in a patch) is absorbed through the skin
- advantage: drug dosage is continuous and long-acting
- disadvantage: product is expensive and may cause local irritation (due to adhesive component)
- examples: Duragesic Patch (narcotic)
  Nicoderm Patch (nicotine)
  Estraderm Patch (estrogen)

d. rectal (PR)

- drug (in suppository form) is inserted into the rectum and is absorbed through mucous membranes into the bloodstream
- advantage: route may be used for unconscious or vomiting patients
- disadvantage: drug may be incompletely or irregularly absorbed
- examples: Tylenol Suppository (analgesic / antipyretic)
  Compazine Suppository (antinauseant)

e. inhalation

- drug is inhaled as a gas or aerosol
- route is usually intended to allow aerosolized drug to act directly on lung tissue (e.g., bronchodilators)
- advantage: inhaled drug produce a rapid onset of action
- disadvantage: inhaled drugs may irritate lung tissue
- examples: Primetine Mist (bronchodilator)
  Marijuana (euphoriant)

f. intranasal

- drug is absorbed through the mucous membranes in nasal passages into the bloodstream
- examples: Miacalcin Nasal Spray (osteoporosis)
  Afrin Nasal Spray (nasal congestion)
g. parenteral: (1) intravenous, (2) intramuscular, & (3) subcutaneous

- drug response: IV > IM > SQ
- advantages:
  - produces a more rapid response than oral or rectal routes
  - avoids unpredictable absorption processes of GI tract
  - useful in unconscious or uncooperative patients
- disadvantages:
  - requires sterile conditions to prevent infections
  - more costly than other routes of administration
  - once injected, a drug cannot be retrieved
  - pain at the injection site

(2) Characteristics of Drug Absorption: Gastrointestinal (GI) Tract

a. drugs must be relatively lipid-soluble to pass through the membrane lining of the GI tract
b. drugs exist either in lipid-soluble (non-charged, non-polar, non-water-soluble, anionic, etc...) form or non-lipid-soluble form depending on their chemical (pH) environment
c. the pH environment changes along the GI tract

i. stomach (highly acidic)
   - favors absorption of weakly acidic drugs
   - aspirin (weak acid) → converted to non-charged molecule in stomach (strongly acidic) → absorbed through the lipid membrane of the stomach

ii. small intestine (slightly alkaline)
   - favors absorption of weakly basic drugs
   - small intestine is major site of drug absorption due to enormous surface area

d. bioavailability

- describes what proportion of the administered drug is available to produce a pharmacologic response

- factors influencing drug bioavailability include:

  i. drug dissolution
     - inert ingredients (binders, disintegrators, lubricants, buffers, etc...), contained in a tablet, determine how rapidly and completely the drug will dissove and will be absorbed though the GI tract
factors influencing drug bioavailability (continued):

ii. GI tract

- the presence of food may affect the dissolution and absorption of drugs
  - example: tetracycline (TCN) + dairy products $\rightarrow$ TCN binds to calcium $\rightarrow$ unabsorbed TCN excreted in feces

- achlorohydria (deficiency or absence of gastric HCl)
  - prevents gastric absorption of acidic drugs
  - prevents dissolution of basic drugs

- deficiency in pancreatic and intestinal secretions $\rightarrow$
  $\rightarrow$ prevents dissolution of enteric-coated tablets $\rightarrow$
  $\rightarrow$ tablets excreted unabsorbed in feces

B. Drug Distribution

- the degree of drug distribution depends on the physical and chemical properties of a drug and its ability to penetrate cell membranes, capillaries, blood-brain barrier, placenta, etc...

(1) Blood-Brain Barrier (BBB)

- only very lipid-soluble drugs and very small molecules are capable of penetrating the tight junction of cells which comprise the BBB to exert a pharmacologic effect on the brain
  - example: heroin exerts a greater pharmacologic effect on the brain than morphine because of its greater lipid-solubility

(2) Plasma Protein Binding

- many drugs, when circulating in plasma, will bind reversibly with plasma proteins (albumin, glycoproteins, and lipoproteins)
- the plasma protein binding profile of a drug will determine the extent of its drug distribution and elimination rate
- only unbound or "free" drug may:
  - diffuse through capillary walls
  - produce a pharmacologic effect
  - be metabolized
  - be excreted
B. Drug Distribution

(2) Plasma Protein Binding (continued)

- since only free drug is capable of being excreted, some bound drug dissociates from plasma protein to reestablish the equilibrium between free and bound drug → the net effect: “circulating drug reservoir” → prolongs duration of action of a drug
- drugs which compete for the same plasma protein binding site may displace each other → drug-drug interaction

  • example: warfarin (Coumadin), an anticoagulant, is 99% bound to albumin; aspirin, also bound to albumin, may displace warfarin from its binding site and increase “free” warfarin blood levels → increase warfarin pharmacologic effect → increase bleeding potential

C. Drug Metabolism (Drug Biotransformation)

- complex liver enzyme system → converts lipid-soluble drugs to water-soluble metabolites → eliminated by the kidneys

(1) “First-Pass Effect” (Liver)

- substances (drugs, toxins, foods, etc...), absorbed into the bloodstream from the GI tract, enter the liver via the hepatic portal vein before entering the general circulation
- the “first-pass effect” allows the liver to metabolize or inactivate drugs and potentially harmful substances before they are distributed throughout the body
- drugs are converted into less active or inactive metabolites by the liver

  heroin (more potent) → morphine (less potent)

(2) Induction / Inhibition of Drug Metabolism

- liver enzymes, which metabolize drugs, may be induced or inhibited by other drugs → drug-drug interactions
  
  a. induction of enzymes

  • smoking (nicotine) → induces metabolism of theophylline (bronchodilator) → decreases serum levels of theophylline → wheezing (due to subtherapeutic levels)
(2) Induction / Inhibition of Drug Metabolism (continued)

b. inhibition of enzymes

- cimetidine (Tagamet) inhibits the metabolism of theophylline → increases theophylline serum levels → theophylline toxicity

D. Drug Elimination

- 3 main routes of drug elimination → kidneys, liver, and bowel
- most drugs are excreted as active, partially active, or inactive metabolites by the kidneys

(1) Elimination in the Feces

- metabolized drug (e.g., erythromycin) excreted by the liver into bile → drug eliminated in feces
- enterohepatic recirculation: metabolized drug is secreted in bile → enters small intestine → reabsorbed into the bloodstream from small intestine → returned to the liver → secreted in bile

(2) Elimination by Kidneys After Drug Metabolism

- liver metabolizes drugs into more polar compounds (glucuronidation, hydroxylation, acetylation) → polar drugs more readily excreted by kidneys

(3) Elimination by Kidneys Directly into the Urine

- drugs may be excreted in the urine by glomerular filtration or tubular secretion

(4) Drug Elimination and Age Considerations

- infants → underdeveloped abilities to metabolize and excrete drugs → greater sensitivity to drugs
- elderly → impaired ability to metabolize and excrete drugs → greater sensitivity to drugs
E. Geriatric Considerations

(1) Absorption

- elderly → decreased cardiac output (30% by age 65) → decreased blood flow (40 - 45%) to GI tract → decreased drug absorption / slower rate of drug absorption

(2) Distribution

- elderly → decreased production of albumin → decrease in serum albumin (approx. 20%) → decrease in albumin-bound drug → increase in "free" drug plasma levels → increased drug effects

(3) Metabolism

- elderly → reduced hepatic enzyme activity + reduced hepatic blood flow (due to decreased cardiac output) → reduced ability to metabolize drug → increased duration and effect of drug
  - example: at age 20, diazepam (Valium) half-life = 20 hours
    at age 80, diazepam half-life = 90 hours

(4) Kidney Excretion

- it has been estimated that kidney function decreases by 10% per decade of life from age 20
F. Overview of Pharmacodynamics & Pharmacokinetics

**DRUG ADMINISTRATION**
(e.g., parenteral, oral, etc.)

**DRUG ABSORPTION**
(from site of administration)

**PLASMA**

**BOUND DRUG**  ↔  **FREE DRUG**

**TISSUE STORAGE**
(e.g., body fat)

**SITE OF ACTION**
(e.g., cell receptors)

**METABOLISM**
(e.g., liver, GI tract, etc.)

**EXCRETION**
(e.g., kidney, feces, etc.)
I. Dose-Response Curves

- demonstrates that a certain dose is required to achieve a response
- the degree of pharmacological response (measured in percentage of maximum biological effect) is plotted on linear scale on the vertical axis; whereas, the dose of the drug is measured is plotted on log scale on the horizontal axis
- the plateau is the part of the curve where increasing drug dose does not increase pharmacological (therapeutic) response

![Graph 1: Log dose-response curve](image1.png)

- example: log dose-response curves for effects of digoxin (drug used in CHF)
  - curve A: increased force of contraction of heart (therapeutic effect)
  - curve B: nausea
  - curve C: visual disturbances
  - curve D: cardiac arrhythmias
  - curve E: ventricular fibrillation → death

![Graph 2: Log dose-response curves for effects of digoxin](image2.png)
II. Time Course of Drug Action

- **onset of action**: the time, after a drug is administered, to achieve a drug serum concentration required to produce a detectable response \((t_0 \rightarrow t_1)\)
- **time to peak**: the time required for a drug to achieve its highest therapeutic serum concentration \((t_0 \rightarrow t_2)\)
- **duration of action (DOA)**: the amount of time a drug is present in adequate serum concentration necessary to produce a therapeutic effect \((t_1 \rightarrow t_3)\)
  - DOA depends on the rate of drug absorption and elimination
- **half-life \((t_{1/2})\)**: the amount of time required for elimination processes to reduce the drug serum concentration by one-half

III. Oral vs Intravenous Graph

graph 3: time course of drug action

graph 4: PO vs IV Curves
IV. Continuous vs Intermittent Drug Administration

IV. Other Concepts

(a) loading dose
(b) maintenance dose
(c) steady-state drug concentration
(d) peaks & troughs
(e) volume of distribution
V. Estimated Creatinine Clearance (for drug dosing considerations)

A. Calculation of Ideal Body Weight (IBW)

1. Female

\[ IBW = (2.3 \times \text{inches above 5'}) + 45.5 \text{ kg} \]

2. Male

\[ IBW = (2.3 \times \text{inches above 5'}) + 50 \text{ kg} \]

B. Creatinine Clearance (CrCl) Formula

\[
CrCl \ (\text{ml/min}) = \frac{(140 - \text{Age}) \times IBW}{sCr \times 72}
\]

(sCr = serum creatinine level)

\[ CrCl_{female} = CrCl \times 0.85 \]

C. Adjusted Body Weight (ABW)

\[ ABW = IBW + 0.4 (\text{Actual Body Wt} - IBW) \]