SUMMARY OF CHAPTER NO. 06 & 07 OF COMPREHENSIVE PHARMACY REVIEW 7TH EDITION

6. BASIC PHARMACOKINETICS

Reaction rate: velocity of the reaction

Reaction order: way in which the drug (reactant) affects the rate

Zero order reaction: drug concentration changes with time at a constant rate.

Rate constant = Ko (concentration / time; mg/ml/hr).

Linear correlation of concentration vs. time with slope=Ko and intercept = Co.

First order reaction:

change of concentration with time is the product of the rate constant and concentration of the remaining drug.

Drug concentration decreases by a fixed percent in each time unit. Linear correlation of log concentration with time.

Rate constant (K) = 1/hour.

Half life t1/2=0.693/k.

Models and compartments

Model: mathematical description to express quantitative relations in a biological system.

Compartment: group of tissues with similar blood flow and drug affinity.

Drug distribution

Drugs distribute quickly to tissues with ↑ blood flow

Drug cross capillaries by passive diffusion and hydrostatic pressure.

Drugs easily cross the capillaries of the kidney glomerulus.

Brain capillaries are surrounded by glial cells forming a thick lipid membrane (BBB) --→ ↓ diffusion of polar and ionic hydrophilic drugs.

Tissue accumulation due to drug/tissue physicochemical or affinity.

Lipid soluble drug → accumulate in adipose (fat) tissue

Tetracycline → accumulate in bone (calcium Complexation).

Plasma protein binding: results in a big complex → can't cross membranes. **Albumin:** major plasma protein for drug binding.

Alpha1-glycoprotein: binds basic drugs (e.g. propranolol) in the plasma. ↑ bound drugs (e.g. phenytoin) can be displaced by other ↑ bound drug → ↑ free unbound drug → in effect / toxicity.

One-compartment model

Intravenous bolus injection

Very rapid drug entry. Rate of absorption is negligible.

Entire body is one compartment → all tissue equilibrate rapidly.

Drug elimination: ***first*** order kinetics. Elimination rate constant = renal excretion rate constant + metabolism (biotransformation) rate constant

Some controlled release oral drugs have ***zero*** absorption rate constant.

Apparent volume of distribution (Vd): hypothetical volume of body fluid in which drug is dissolved. Vd is needed to estimate amount of drug in the body (Db) relative to concentration in plasma (Cp).

Cp = Db / Vd

More drug distribution into tissues → ↓ Cp → ↑ Vd

Single oral dose

Rapid absorption then elimination, both with ***first*** order kinetics.

Time to reach max concentration (tmax) depends only on absorption and elimination rate constants but not on Vd or Db.

AUC: calculated using trapezoidal rule by integrating the plasma drug concentration over time. AUC depends on Do, Vd, elimination K but not absorption K.

Lag time: at the beginning of systemic drug absorption, e.g. due to delay in gastric emptying.

Intravenous infusion

Absorption: ***zero*** order. Elimination: ***first*** order (when infusion stops)

Steady state concentration (Css): target plateau drug concentration where fraction of drug absorbed = fraction of drug eliminated.

Loading dose (DL): initial IV bolus dose to produce Css as rapidly as possible. Start IV infusion at the same time.

DL: amount of drug that, when dissolved in the apparent Vd, produces the desired Dss. Reaching 07% of Css without DL takes ~ t1/2. Time to reach Css depends on the drug elimination half life.

IV infusion: ideal for drugs with narrow therapeutic window (controls Cp).

Intermittent intravenous infusion

Drug is infused for short periods to prevent accumulation and toxicity.

Used for aminoglycosides (e.g. gentamicin).

Multiple doses

Drug is given intermittently in multiple-dose regimen for continuous or prolonged therapeutic activity to treat chronic disease.

Give new dose before previous dose completely eliminated → Cp accumulation → ↑ to Css.

At steady state: Cp fluctuations between a-max and a-min ($C^{\infty}_{min\text{-}max}$).

Superposition principle: assumes that previous drug doses have no effect on subsequent doses → total Cp = cumulative residual Cp from each previous dose.

Dosing rate = dose size (Do) / dose interval (e.g. X mg/hr).

Same dosing rate → same average Css but may be different ($C^{\infty}_{min\text{-}max}$).

Some AB → multiple rapid IV bolus injections.

Oral immediate release drug products (multiple doses) → rapid absorption, slow elimination.

Maintenance dose (DM): after loading dose to maintain Cp at Css.

If DM dosing interaval = elimination t1/2 → DL = 2 x DM

Multi-compartment models

Drug distributes into different tissue groups at different rates. Tissues with ↑ blood flow equilibrate rapidly with the drug.

Two-compartment model (IV bolus): First, rapid distribution into highly perfused tissue (**central compartment**) → rapid decline in Cp (**distribution phase**). Both are first-order processes. Then, slow distribution into peripheral tissues (**tissue compartment**) → slow decline in Cp after equilibration (**elimination phase**).

Vd = Vd at steady state + central + tissue compartment volumes.

Two-compartment model (oral): two-compartment ONLY if absorption is rapid but distribution is slow.

Models with additional compartments: example of a third compartment: deep tissue space. If frequent interval dosing → third compartment accumulation.

Elimination rate constant: two constants; one for elimination from central compartment, the other for elimination after complete distribution.

Nonlinear pharmacokinetics

Also known as **capacity-limited, dose-dependent, or saturation PK.**

Result from the saturation of an enzyme of carrier-mediated system.

Do not follow first-order kinetics as the dose ↑.

AUC or drug excreted in urine are not proportional to dose

Elimination t1/2 may ↑ at ↑ doses.

Michaelis-Menten equation: describe velocity of enzyme reactions in nonlinear PK. It described rate of change of Cp after IV bolus. If Cp is ↑ → the equation is a zero-order rate of elimination. If Cp is ↓↓ → first-order.

Note that first-order PK = linear PK

Clearance

Total body clearance (Cl_T)

Cl_T = drug elimination rate / Cp = K x Vd

Cl_T and Vd are independent variables. T1/2 is a dependent variable.

A constant volume of the Vd is cleared from the body per unit time.

First order PK: Cl_T = renal clearance + non-renal (hepatic) clearance

↓ Cl_T → ↑ t1/2. ↑ Vd □ ↑ t1/2

Renal drug excretion

Major route of elimination for: polar drugs, water-soluble drugs, drugs with ↓ MWt (<500), drugs that are biotransformed slowly.

Glomerular filtration: passive process that filters small molecules. Drugs that are bound to plasma proteins are too big to be filtered. **Creatinine** and **inulin** undergo only glomerular filtration (not tubular secretion or reabsorption) → used to measure glomercular filtration rate (GFR).

Tubular reabsorption: passive process that follow Fick's first law of diffusion to reabsorb lipid-soluble and non-ionized weak electrolytes drugs back to the systemic circulation. If ionized or water-soluble → excreted in the urine. **Diuretic** →↑ urine flow → ↓ time for reabsorption → ↑ drug excretion.

Active tubular secretion: carrier-mediated active transport system that requires energy. Two systems: for weak acids and weak bases. Competitive nature: e.g. probenecid (weak acid) compete for the same system as penicillin □ ↓ penicillin excretion. Another example: p-aminohippurate. Measure using **effective renal blood flow (ERBF).**

Renal clearance (Cl_R)

It is the volume of drug in the plasma remove by the kidney per unit time.

Cl_R = rate of drug excretion / Cp = ml/minute.

Clearance ratio: relates drug clearance to inulin clearance (GFR). If = 1 → filtration only. If < 1 → filtration + reabsorption. If > 1 → filtration + active tubular secretion.

Hepatic clearance

Volume of drug-containing plasma cleared by the liver per unit time.

Measurement of hepatic clearance (Cl_H)

Main mechanism for non-renal clearance. Measured indirectly (difference between total and renal clearance).

Cl_H = hepatic blood flow x extraction ratio.

Extraction ratio: drug fraction irreversibly removed by an organ or tissue as the drug-containing plasma perfuses the tissue.

Blood flow, intrinsic clearance, protein binding

All these factors affect hepatic clearance.

Blood flow: to the liver is ~ 1.5 L/min. After oral GI absorption → to mesenteric vessels → to hepatic portal vein → through the liver → to hepatic vein → to systemic circulation.

Intrinsic clearance: ability of the liver to remove the drug independent of blood flow due to inherent ability of the biotransformation enzymes (oxidases) to metabolize the drug as it enters the liver. This is affected by enzyme inducers (Phenobarbital, tobacco) and inhibitors (cimetidine, lead).

Protein binding: bound drugs are not easily cleared by the liver or kidney. Only free drug crosses the membrane into the tissue and is available to metabolizing enzymes.

Biliary drug excretion

Active transport (secretion) process. Separate systems for weak acids and weak bases.

Excretes ↑ MWt drugs (>500) or polar drugs (digoxin, reserpine, glucuronide conjugates).

Drugs may be recycled by **enterohepatic circulation.** GI absorption → mesenteric vessels → hepatic portal veins → liver → secrete to the bile →store in gallbladder →empty into the GI through the bile duct (recirculation).

First pass effect (pre-systemic elimination)

Portion of oral drugs may be eliminated before systemic absorption due to rapid drug biotransformation by liver enzymes.

Measure absolute bioavailability (F). If $F < 1$ → some drug was eliminated before systemic absorption.

Common for drug with high liver extraction ratio.

If ↑ first-pass effect → ↑ dose (e.g. propranolol, penicillin), different route (e.g. nitroglycerin, insulin), or modified dosage form (e.g. mesalamine).

Non-compartment models

Some PK parameters can be estimated with non-compartment methods using comparison of the AUCs.

Mean residence time (MRT): average time for the drug molecules to reside in the body. Called *Mean Transit Time or Sojourn Time.* It depends on the route of administration. Assumes elimination from the central compartment. MRT = total residence time of all drug molecules in the body / total number of drug molecules.

Mean absorption time (MAT): difference between MRT and MRTIV and an extravascular route.

Clearance: volume of plasma cleared of the drug per unit time.

Steady-state volume of distribution (Vss): amount of drug in the body at steady sate and the average steady-state drug concentration.

Clinical pharmacokinetics

The application of PK principles to the rational design of an individualized dosage regimen.

Objectives: maintenance of an optimum drug concentration at the receptor site to produce effect for the desired period, and minimization of SE.

Toxicokinetics

Application of PK principles to the design, conduct, and interpretation of drug sate evaluation studies.

Used to validate dose-related exposures in animals in preclinical drug development to predict human toxicity.

Clinical toxicology: study of SE of drugs and poisons. PK in intoxicated patient (↑↑ dose) may be very different from a patient taking therapeutic doses.

Population pharmacokinetics

Study of sources and correlation of variability in drug concentration in the target patient population. Includes PK and non-PK parameters such as age, gender, weight, creatinine clearance, concomitant disease.

7. BIOAVAILABILITY AND BIOEQUIVALENCE

Definitions

Bioavailability: measurement of the rate and extent to which the active moiety becomes available at the site of action. It is also the rate and extent of active drug that is systemically absorbed.

Bioequivalent drug products: a generic drug product is considered bioequivalent to the reference brand drug product if both products are pharmaceutical equivalents and have statistically the same bioavailability for the same dose, in the same chemical form, similar dosage form, by same route of administration, under same experimental conditions.

Generics: requires abbreviated NDA for FDA approval after patent expiration. Must be a therapeutic equivalent but may differ in shape, scoring, packaging, excipients, expiration dates, labeling.

Pharmaceutical equivalents: drug product that contain the same active drug, same salt, ester or chemical form, same dosage form, identical in strength and route of administration. May differ in release mechanism, shape, scoring, packaging, excipients.

Reference drug product: usually the currently marketed brand name with full NDA and patent protection.

Therapeutic equivalent drug products: are pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile under same conditions.

Pharmaceutical alternatives: are drug products that contain the same therapeutic moiety but are different salts, ester or complexes or are different strength or dosage forms (tablet vs cap, instant release vs SR).

Bioavailability and bioequivalence

Acute pharmacologic effect

Examples: change in heart rate, blood pressure, ECG, clotting time, Forced Expiratory Volume (FEV1). Alternative to plasma concentration when that is not possible or inappropriate. Measure effect vs. time.

Onset time: time from drug administration till achieving the minimum effective concentration (MEC) at the receptor site as evidenced by pharmacological response. **Intensity:** proportional to the # of receptors occupied by the drug up to a maximum pharmacological effect, which may occur before, at or after peak drug absorption. **Duration of action:** time for which the drug concentration remains above MEC. **Therapeutic window:** concentration between the MEC and minimum toxic concentration (MTC). As concentration ↑ -→ other receptor interactions lead to SE. In vitro test (e.g. dissolution) can be used instead if statistical correlation to in vivo data has been established. Example: dermato-PK for topical drugs for local effect.

Plasma drug concentration

Most common method for measuring systemic bioavailability.

Time for peak plasma concentration (Tmax): relates the rate constant for drug absorption and elimination. Absorption depends on the dosage form and formula, while elimination is only drug dependent.

Peak plasma concentration (Cmax): Cmax at Tmax relates to the intensity of pharmacological response. Ideally Cmax should be within the therapeutic window.

AUC vs time: relates the amount or extent of systemic drug absorption. AUC is calculated using the trapezoidal rule, expressed as mg.hr/ml

Urinary drug excretion

Accurate method if the active moiety is excreted unchanged in ↑ quantities in urine. **Cumulative amount of active drug excreted in urine** is related to extent of systemic drug absorption. **Rate of drug excretion** is related to rate of systemic absorption.

Time for complete excretion relates to the total time for complete systemic absorption and excretion.

Relative and absolute bioavailability

Relative bioavailability: systemic availability of the drug from a dosage form as compared to reference standard given by the same route. It is a ratio of the AUCs (maximum is 1 or 100%). Very important for generic bioequivalence studies.

Absolute bioavailability (F): fraction of drug that is systemically absorbed. It's the ratio of AUC for oral dosage form / AUC for IV. A parenteral IV drug solution has F = 1.

Bioequivalence for solid dosage forms

Design of bioequivalence studies

Guidance provided by Division of Bioequivalence, Office of Generic Drugs, FDA. All studies are done with healthy subjects.

Fasting study: blood samples are taken at zero time, and appropriate intervals to obtain adequate description of concentration vs. time profile.

Food intervention study: required if bioavailability is known to be affected by food. Give products immediately after a standard high fat content breakfast.

Multiple dose steady-state study: required for extended release products in addition to single-dose fasting and food intervention study. Measure three consecutive days of trough concentrations (Cmin) to ascertain steady state. Last morning dose is given after overnight fast, continue fasting for 2 hours. Take blood samples.

In vitro bioequivalence waiver: a comparative in vitro dissolution may be used instead for some immediate release oral dosage forms. No bioequivalence study is required for certain solution products (oral, parenteral, ophthalmic).

PK data evaluation

Single dose studies: calculate AUC to last quantifiable concentration, AUC to infinity, Tmax, Cmax, elimination rate constant (K), elimination half life (t1/2).

Multiple dos studies: steady state AUC, AUC to last quantifiable concentration, Tmax, Cmax, Cmin, % fluctuation (Cmax-Cmin / Cmin).

Statistical data evaluation

Drug considered bioequivalent if difference from reference is < -20% or +25%. ANOVA is done on log transformed AUC and Cmax data. The 90% confidence interavals of the means of AUC and Cmax should be 80-125% of the reference product.

Drug production selection

Generic drug substitution

It's dispensing generic drug in place the prescribed product. The substituted drug has to be a therapeutic equivalent.

Prescribability: current basis for FDA approval of therapeutic equivalent generic product. It's measurement of average bioequivalence where test and reference population means are statistically the same.

Switchability: assures that the substituted product produces the same response in the individual patient. It's the measurement of the individual bioequivalence including intra-subject variability and subject-by-formulation effects.

Therapeutic substitution

The process of dispensing a therapeutic alternative. For example: dispensing amoxicillin for ampicillin. The substituted drug is usually in the same therapeutic class (e.g. calcium channel blockers) and is expected to have a similar clinical profile.

Formulary issues

A formulary is a list of drugs. **Positive formulary:** lists all drugs that may be substituted. **Negative formulary:** lists drugs which can't be substituted. **Restrictive formulary:** lists only drugs that may be reimbursed without justification by the prescriber. States provide guidance for drug product selection through formulary.

FDA annually publishes *Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book").* It is also published in the USP/DI Volume III.

Orange Book Codes: A Rated: drug products that are considered therapeutically equivalent. **B Rated:** drug products that are not considered therapeutically equivalent. **AB Rated:** products meeting bioequivalence requirements.