



THERAPEUTIC DRUG MONITORING (TDM)

5TH STAGE, 2ND SEMESTER

Reference Texts: Applied Clinical Pharmacokinetics, by
Larry A. Bauer. (Latest edition)

Additional references include but not limited to: Clinical
Pharmacokinetics Concepts and Applications, by Malcolm
Rowland and Thomas Tozer (Latest edition)

م.د شيرين محمد مكي الحسيني

No	Lecture title	hours
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2	Review of basic pharmacokinetic (PK)-	2
3	Review of basic pharmacodynamic (PD)	1
4	Clinical PK equations and calculations	3
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6	Clinical PK/PD for Antibiotics (e.g., Aminoglycosides, Vancomycin	4
7	Clinical PK/PD for Cardiovascular agents (e.g., Digoxin, Lidocaine, Procainamide/N-Acetyl Procainamide	4
8	Clinical PK/PD for Anticonvulsants (e.g., Phenytoin, Carbamazepine, Valproic Acid, Phenobarbitone/Primidone, Ethosuxsimide	6
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Clinical Pharmacokinetic and Pharmacodynamics Concepts

- **Pharmacokinetics (PK):** is the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs.
- **Pharmacodynamics (PD):** is the relationship between drug concentration and pharmacological response.
- **Clinical pharmacokinetics:** is the application of pharmacokinetic concepts and principles in humans in order to design individualized dosage regimens which optimize the therapeutic response and minimize the adverse drug reaction.

Therapeutic drug monitoring (TDM)

- TDM is the clinical laboratory measurement of drug concentrations in plasma, serum or blood and using this information to individualize the dosage and maintain the drug concentrations within a target therapeutic range.
- Laboratories routinely measure patient serum or plasma samples for many drugs, including antibiotics (eg, aminoglycosides and vancomycin), antiepileptics (eg, phenytoin, carbamazepine, valproic acid, phenobarbital, and ethosuximide), antiarrhythmics (eg, lidocaine, procainamide, quinidine and digoxin), immunosuppressants (eg, cyclosporine and tacrolimus), and others (theophylline, lithium).

Criteria of drugs suitable for TDM

- 1- A good relationship exists between plasma concentrations and clinical effects. This relationship allows to predict pharmacologic effects with changing plasma drug concentrations.
- 2- The drug should have a narrow therapeutic range.
- 3- At any given dose, there is large interindividual variability in plasma concentration of the drug and/or its metabolites.
- 4- The therapeutic effect cannot be readily assessed by the observation of the clinical parameters i.e. a precise clinical end point is not available (e.g. anticonvulsants, anti-arrhythmics, antidepressants etc.).
- 5- An appropriate cost-effective analytical test must be available for the analysis of drug and/or its active metabolites.

Indications for TDM

- 1- Monitoring adherence to drug therapy.
- 2- Individualizing therapy (during early treatment and during dosage changes).
- 3- Diagnosing undertreatment.
- 4- Avoiding toxicity.
- 5- Monitoring and detecting drug interactions.
- 6- Guiding withdrawal of drug therapy.

Steady state condition

- When drugs are given on a constant basis (e.g. a continuous intravenous infusion or an oral medication given every 12 hours), serum drug concentrations increase until the rate of drug administration equals the rate of drug metabolism and excretion.
- At that point, serum drug concentration reaches a constant value and this equilibrium condition is known as steady state.
- The only factor that effect on time required to reach steady state is the half-life of the drug since the time required to reach to steady state equal to $(3-5) \times \text{half-life}$.
- Steady state condition is extremely important because usually steady-state serum concentrations are used to assess patient response and compute new dosage regimens.

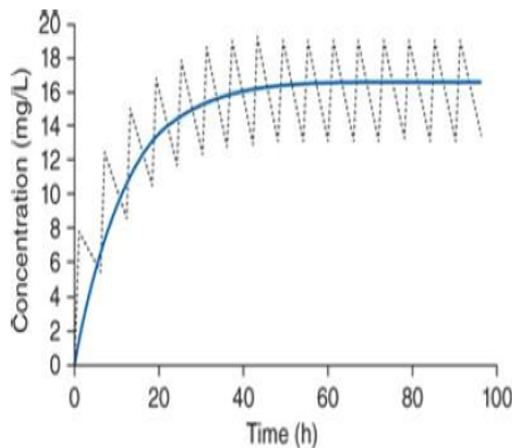


Figure: Steady state condition. The lines show serum concentrations in a patient receiving a drug intravenously (solid line) and orally (dashed line).

Linear versus non-linear pharmacokinetics

- If a plot of steady state concentration versus dose yields a straight line, the drug is said to follow **linear pharmacokinetics**.
- In this situation, steady-state serum concentrations increase or decrease proportionally with dose (e.g., a 50% increase in dose yields a 50% increase in steady-state concentration).
- Most drugs follow linear pharmacokinetics.
- When steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow **non-linear pharmacokinetics**.
- When steady-state concentrations increase more than expected after a dosage increase, the most likely explanation is that the metabolism of the drug has become saturated.
- This phenomenon is known as saturable or Michaelis-Menten pharmacokinetics.
- Both phenytoin and salicylic acid follow Michaelis-Menten pharmacokinetics.

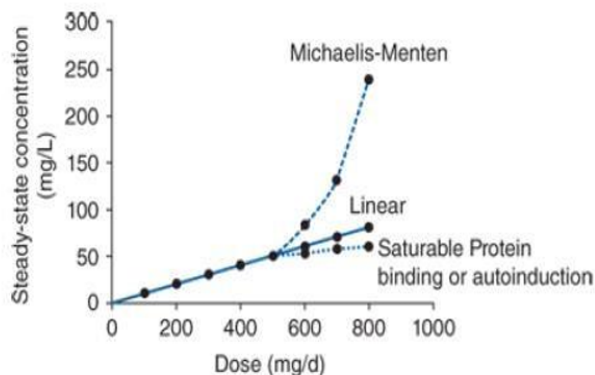


Figure: Linear pharmacokinetics (solid line). Michaelis-Menten pharmacokinetics (upperdashed line). Saturable plasma protein binding or autoinduction (lower dashed line).

- When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations:
 - 1- Some drugs, such as valproic acid and disopyramide, saturate plasma protein binding sites so that as the dosage is increased, the steady-state serum concentrations increase less than expected.
 - 2- Other drugs, such as carbamazepine, increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than expected.
- This process is known as autoinduction of drug metabolism.
- Drugs that exhibit non-linear pharmacokinetics are often very difficult to dose correctly.

Clearance

- **Definition:** clearance (Cl) is the volume of serum or blood completely cleared of the drug per unit time. Thus, the dimension of clearance is volume per unit time, such as L/h or mL/min.
- The liver is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug elimination.
- The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile.
 - $CL = DOSE / AUC$
 - $CL = K_e * V$

- Clearance is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (C_{ss}):

$$\bullet \text{ MD} = \text{C}_{\text{ss}} \cdot \text{Cl}$$

- The clearance for an organ, such as the liver or kidney, is determined by the blood flow to the organ and the ability of the organ to metabolize or eliminate the drug.

- Liver blood flow (LBF) and renal blood flow (RBF) are each about 1–1.5 L/min in adults with normal cardiovascular function.
- The ability of an organ to remove or extract the drug from the blood or serum is usually measured by determining the extraction ratio (ER), which is the fraction of drug removed by the organ, and is computed by measuring the concentrations of the drug entering (C_{in}) and leaving (C_{out}) the organ:

$$\text{ER} = (\text{C}_{\text{in}} - \text{C}_{\text{out}}) / \text{C}_{\text{in}}$$

- The drug clearance for an organ is equal to the product of the blood flow to the organ and the extraction ratio of the drug. Therefore, hepatic clearance (Cl_H) for a drug would be:

$$\text{Cl}_H = \text{LBF} \cdot \text{ER}_H$$

and renal clearance (Cl_R) for a medication would be:

$$\text{Cl}_R = \text{RBF} \cdot \text{ER}_R$$

- The total clearance for a drug is the sum of the individual clearances for each organ that extracts the medication.
- For example, the total clearance (Cl) for a drug that is metabolized by the liver and eliminated by the kidney is the sum of hepatic and renal clearance for the agent: $\text{Cl} = \text{Cl}_H + \text{Cl}_R$

Hepatic clearance

- Hepatic clearance depends on the intrinsic ability of the enzyme to metabolize a drug (intrinsic clearance; Cl'_{int}); the unbound fraction of drug present in the blood (free fraction); and liver blood flow.
- The relationship between the three physiological factors and hepatic drug clearance is:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

- Where **LBF** is liver blood flow, **fB** is the fraction of unbound drug in the blood, and **Cl'int** is intrinsic clearance.
- For drugs with a low hepatic extraction ratio ($ERH \leq 0.3$), hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance:
 - $Cl_H = f_B \cdot Cl'_{int}$

- In this case, drug interactions that displace drug molecules bound to proteins will increase the fraction of unbound drug in the blood ($\uparrow f_B$); more unbound drug molecules will be able to leave the vascular system and enter hepatocytes where the additional unbound drug will be metabolized, and hepatic drug clearance will increase.
- Additionally, drug interactions that inhibit or induce the cytochrome P-450 enzyme system (decreasing or increasing Cl'_{int} , respectively) will change the hepatic clearance of the medication accordingly.
- The hepatic clearance of drugs with low extraction ratios does not change much when liver blood flow decreases secondary to liver or cardiac disease.
- Examples of drugs with low hepatic extraction ratios are valproic acid, phenytoin, and warfarin.

- For drugs with high hepatic extraction ratios ($ERH \geq 0.7$), hepatic clearance is mainly a function of liver blood flow:

$$Cl_H = LBF$$

- The rate limiting step for drug metabolism in this case is how much drug can be delivered to the liver because the capacity to metabolize drug is very large.
- In this case, hepatic clearance is very sensitive to changes in liver blood flow due to congestive heart failure or liver disease. However, the hepatic clearance of drugs with high extraction ratios does not change much when protein binding displacement or enzyme induction or inhibition occurs due to drug interactions.

Renal clearance

- The physiological determinants of renal clearance are glomerular filtration rate (GFR), the free fraction of drug in the blood or serum (f_B), the clearance of drug via renal tubular secretion (Cl_{sec}), and the fraction of drug reabsorbed in the kidney (FR) in addition to renal blood flow.

$$Cl_R = \left[(f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

Volume of distribution

- **Volume of distribution (V):** is an important pharmacokinetic parameter because it determines the loading dose (LD) that is required to achieve a particular steady state drug concentration immediately after the dose is administered:

$$LD = C_{ss} \cdot V$$

- The volume of distribution is a hypothetical volume that relates drug serum concentrations to the amount of drug in the body. Thus, the dimension of volume of distribution is in volume units, such as L or mL.

- At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) is equal to the quotient of the amount of drug in the body (X) and the volume of distribution:

$$C = X/V$$

- The volume of distribution can be very small if the drug is primarily contained in the blood (warfarin $V = 5-7$ L), or very large if the drug distributes widely in the body and is mostly bound to body tissues (digoxin $V = 500$ L).

- The physiologic determinates of volume of distribution are the actual volume of blood (V_B) and size (measured as a volume) of the various tissues and organs of the body (V_T).
- Therefore, a larger person, such as a 160-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grandmother.
- How the drug binds in the blood or serum compared to the binding in tissues is also an important determinate of the volume of distribution for a drug.

- For example, the reason warfarin has such a small volume of distribution is that it is highly bound to serum albumin so that the free fraction of drug in the blood (f_B) is very small.
- Digoxin has a very large volume of distribution because it is very highly bound to tissues (primarily muscle) so that the free fraction of drug in the tissues (f_T; f_T = unbound drug concentration in the tissue/total tissue drug concentration) is very small.

$$V = CL / k_e$$

- The equation that relates all of these physiologic determinates to the volume of distribution is:

$$V = V_B + \frac{f_B}{f_T} V_T$$

- This equation can help clinicians to understand why a drug has a large or small volume of distribution, or why the volume of distribution might change under various circumstances.
- An example is how the volume of distribution changes when plasma protein binding drug interactions occur. If a drug that is highly bound to plasma proteins is given to a patient, and then a second drug that is also highly bound to the same plasma protein is given concurrently, the second drug will compete for plasma protein binding sites and displace the first drug from the protein.
- In this case, the free fraction in the serum of the first drug will increase ($\uparrow f_B$), resulting in an increased volume of distribution:

$$\uparrow V = V_B + (\uparrow f_B / f_T) V_T$$

Half-life and elimination rate constant

- When drugs that follow linear pharmacokinetics are given to humans, serum concentrations decline in a curvilinear fashion.
- When the same data is plotted on a semilogarithmic axis, serum concentrations decrease in a linear fashion after drug absorption and distribution phases are complete. This part of the curve is known as the elimination phase.
- The time that it takes for serum concentrations to decrease by 1/2 (one-half) in the elimination phase is a constant and is called the half-life ($t_{1/2}$).
- The half-life describes how quickly drug serum concentrations decrease in a patient after a medication is administered, and the dimension of half-life is time (hour, minute, day, etc.).

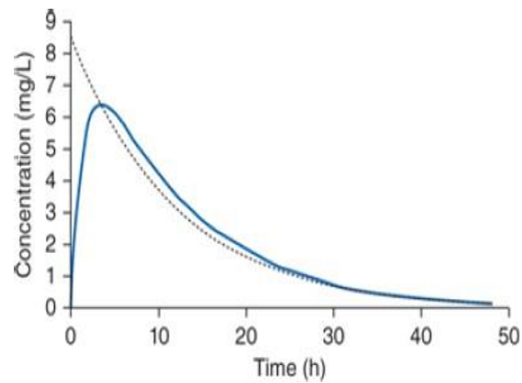


Figure: Serum concentration/time profile for a patient receiving a drug orally (*solid line*) and by intravenous bolus (*dashed line*). When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete.

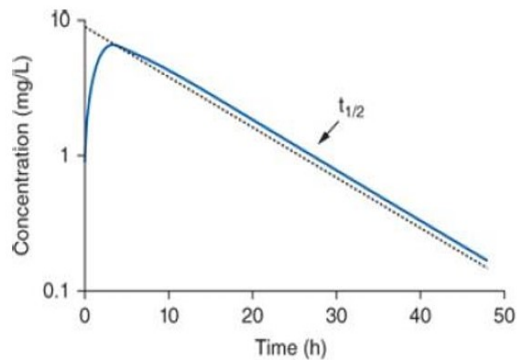


Figure: Data from the previous figure plotted on semilogarithmic axis, serum concentrations decline in a straight line in both cases.

- Another common measurement used to express how quickly drug serum concentrations decline in a patient is the elimination rate constant (k_e).
- The dimension for the elimination rate constant is reciprocal time (hour⁻¹, minute⁻¹, day⁻¹, etc.). It means fraction of remaining removed from the body per unit time.
- If the amount of drug in the body is known, the elimination rate for the drug can be computed by taking the product of the elimination rate constant and the amount of drug in the body (X):

$$\text{Elimination rate} = X \cdot k_e$$

- The half-life and elimination rate constant are related to each other by the following equation, so it is easy to compute one once the other is known:

$$t_{1/2} = 0.693/k_e$$

- The half-life and elimination rate constant are known as dependent parameters because their values depend on the clearance (Cl) and volume of distribution (V) of the agent:

$$t_{1/2} = (0.693 \cdot V)/Cl$$

$$k_e = Cl/V$$

Bioavailability

- When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. The fraction of the administered dose that is delivered to the systemic circulation is known as the bioavailability for the drug and dosage form.
- For drugs that follow linear pharmacokinetics, bioavailability is measured by comparing the total area under the serum concentration time curve (AUC) for the extravascular and intravenous doses.

$$F = AUC_{Po}/AUC_{Iv}$$

- If it is not possible to administer the same dose intravenously and extravascularly, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration:

$$F = (AUC_{Po}/AUC_{Iv}) (Div/Dpo)$$

- Where Div is the intravenous dose and Dpo is the oral dose.

Bioequivalence

- Bioequivalence is achieved when the serum concentration/time curve for the generic and brand drug dosage forms (or two different dosage forms of the same drug) are considered superimposable and identical using statistical tests.
- Concentration/time curves are superimposable when the area under the total serum concentration/time curve (AUC), maximum concentration (C_{max}), and time that the maximum concentration occurs (T_{max}) are identical within statistical limits.
- The ratio of the area under the serum concentration/time curves for the generic (AUC generic) and brand (AUC brand) drug dosage forms is known as the relative bioavailability (F relative), since the reference AUC is derived from the brand name drug dosage form:
 - $F \text{ relative} = \text{AUC}_{\text{generic}} / \text{AUC}_{\text{brand}}$

Thank you

Any questions?

