# *Clinical Pharmacokinetic and Pharmacodynamic Concepts*

## *Introduction*

**Pharmacokinetics** is the study of the absorption, distribution, metabolism, and excretion (ADME) of drugs.

**Pharmacodynamics:** the relationship between drug concentration and pharmacological response.

**Clinical pharmacokinetics** is the application of pharmacokinetic concepts and principles in humans 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 dosage so that drug concentrations can be maintained within a target therapeutic range.

• Laboratories routinely measure patient serum or plasma samples for many drugs, including antibiotics (eg, aminoglycosides and vancomycin), theophylline, antiepileptics (eg, phenytoin, carbamazepine, valproic acid, phenobarbital, and ethosuximide), methotrexate, lithium, antiarrhythmics (eg, lidocaine and digoxin), and immunosuppressants (eg, cyclosporine and tacrolimus).

*Note to remember:*

- Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of patient's drug therapy

- The TDM is study the pharmacokinetic only

## Criteria of drugs suitable for TDM: (Q: When TDM is valuable?) Answer:

1- A good relationship exists between plasma concentrations and clinical effects. This relationship allows the prediction of the pharmacologic effects of changing plasma drug concentrations.

2- The drug should have a narrow therapeutic index. (i.e., The therapeutic concentration is close to the toxic concentration).

3- At any given dose, there is large interindividual variability in the 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 endpoint is not available (e.g., anticonvulsants, anti-arrhythmic, antidepressants, etc.).

5- An appropriate cost-effective analytical test must be available for the analysis of the drug and/or its active metabolites.

**Uses of TDM:**

1. Calculate loading and maintenance drug doses:

A. Loading dose is a large initial dose given to achieve therapeutic drug levels

B. Maintaining dose is a dose given at a fixed amount of dose at fixed intervals to keep drug concentrations within the therapeutic range.

2. Calculate the drug dosage regimen. The dosage regimen is a systemized dosage schedule with two variables

A. The size of each drug dose.

B. The time between consecutive dose administrations.

3. Perform dosage adjustments (for example, in renal and hepatic diseases)

4. Design of dosage form and determination of the route of administration

• Sustained release versus immediate release oral dosage forms.

• parenteral versus oral dosage forms.

5. Perform bioequivalence studies and pharmacokinetic evaluations of drug formulation (excipients).

6. Predict drug-drug and drug-food interactions. (Drugs and food can affect (ADME)

**Pharmacokinetic models**

Pharmacokinetic models are relatively simple mathematical schemes that represent complex physiologic spaces or processes. Accurate PK modeling is important for the precise determination of the elimination rate. The most commonly used pharmacokinetic models are

## 1. One-compartment model

In one compartment model, the body acts as a single uniform compartment into which the drug is administered and from which it is eliminated

• This is the simplistic view of the body in which the drug enters the bloodstream and is then rapidly equilibrated with other parts of the body. This model doesn't predict actual drug concentration in the various tissues but assumes that drug tissue concentration will be proportional to the drug plasma concentration

• If a drug rapidly equilibrates with the tissue compartment, which uses only one volume term, the apparent volume of distribution (V)

• A log scale plot of the serum level decay curve of a one

The compartment model yields a straight line eg aminoglycosides)



Figure 1. One compartment model

## 2. Two-compartment model

Drugs showing a slow equilibration with peripheral tissues are best described with a two-compartment model A log scale plot of the serum level decay curve of a 2-compartment model yields a biphasic line e g vancomycin

## 3. Non-compartment model

Sometimes pharmacokinetic analysis can be conducted without specifying any mathematical models (non-compartmental methods), which is highly dependent on the estimation of total drug exposure Total drug exposure is most often estimated by the area under the curve (AUC) methods.
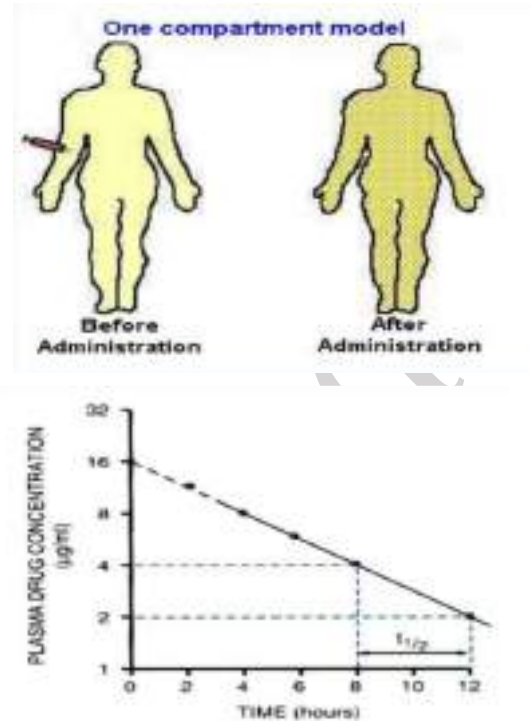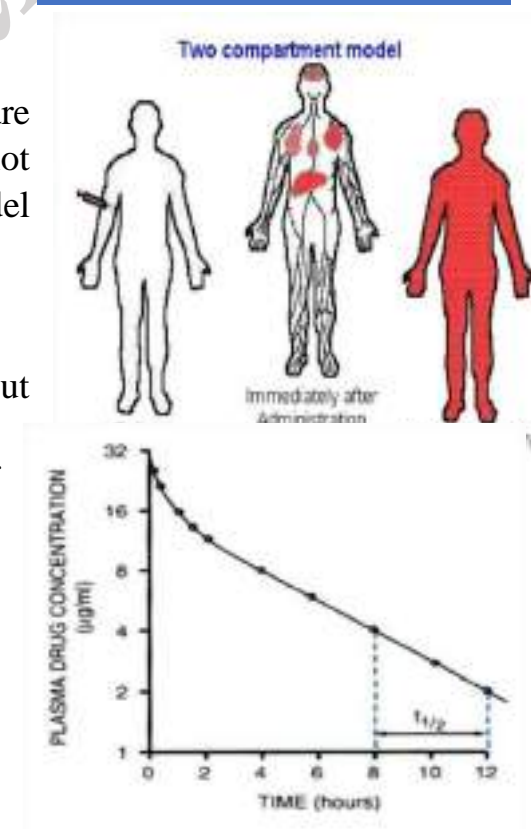


Figure 2. Two compartment model

**Steady-state condition:**

In pharmacokinetics, a steady state refers to a situation where the overall intake of a drug is fairly in dynamic equilibrium with its elimination. In practice, the steady state could be reached mostly after 3 to 5 times the half-life for the drug after regular dosing is started.

Steady-state condition is extremely important because usually steady-state serum or blood concentrations are used to assess patient response and compute new dosage regimens. Figure 3

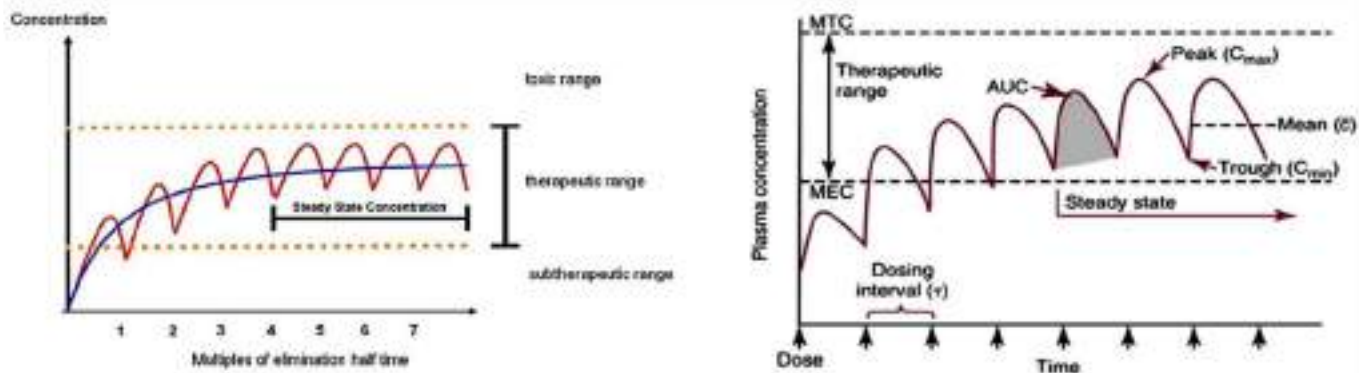> - steady state is affected by $t_{1/2}$



**Figure 3**

**Linear pharmacokinetics: (1$^{st}$ order kinetic)**

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.

- Half-life is independent of concentration, (half-life will remain constant, no matter how high the concentration).
- Clearance is independent of the schedule
- Drug exposure (is not affected by changes in drug schedule

**Non-Linear pharmacokinetics: (Zero order kinetic)**

When steady-state concentrations change disproportionately 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.

Definition: "Kinetics resulting from saturable drug transfer, leading to variation of the Standard kinetic parameters with drug concentration"

When the dose of a drug is increased, we expect that the concentration at a steady state will increase proportionally i.e., if the dose rate is increased or decreased say tow folds, the plasma drug concentration will also increase or decreased tow folds. However, for some drugs, the plasma drug concentration will change either more or less than would expect from a change in dose rate. This is known as non-linear pharmacokinetic behavior and can cause problems when adjusting doses

Nonlinear kinetics is usually due to saturation occurring in one of the pharmacokinetic mechanism's protein binding, hepatic metabolism, drug absorption, auto-induction, or active renal transport of the drug.

| Linear pharmacokinetics | Non-Linear pharmacokinetics |
|---|---|
| Known as dose-independent or conc. independent pharmacokinetics | Known as dose-dependent or conc. dependent pharmacokinetics |
| The absorption, distribution, and elimination of drugs follow 1 order kinetics | At least one of the pharmacokinetic processes (absorption, distribution, and elimination) is saturable (i.e., depending on the mechanism of the equation) |
| Pharmacokinetic parameters such as $t1_{/2}$, total body clearance, and volume of distribution are constant and don't depend on the drug conc. | Pharmacokinetic parameters such as $t_{1/2}$, total body clearance, and volume of distribution are conc. dependent |
| The change in drug dose results in a proportional change in drug conc. | The change in drug dose results in more than proportional or less than proportional change in drug conc. |

**Saturable elimination** above a certain drug concentration, the elimination rates tend to reach a maximal value. Once this maximum capacity is reached, there is no further increase in the elimination rate when plasma drug concentration increases Therefore, in non-linear elimination kinetics drug clearance decreases with increased drug concentration

**Saturable binding or reabsorption** above a certain drug concentration, drug-protein binding, or drug reabsorption in kidney tubules tend to reach maximum capacity. This led to a disproportionate increase in the rate of elimination with increasing drug concentration e.g. With a high dose of vitamin)

**Saturable absorption** above a certain drug concentration at the absorption site, there is no further increase in absorption rate. Therefore the absorption rate constant and possibly the bioavailability decrease with doses lead to concentrations at the absorption site above the maximal absorption capacity.

❖ 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 4.** When doses are increased for most drugs, steady-state concentrations increase proportionally, leading to linear pharmacokinetics (solid line). However, in some cases, proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase more than expected after a dosage increase (upper dashed line), Michaelis Menten pharmacokinetics may be taking place If steady-state concentrations increase less than expected after a dosage increase lower dashed line saturable plasma protein binding or autoinduction are likely explanations.
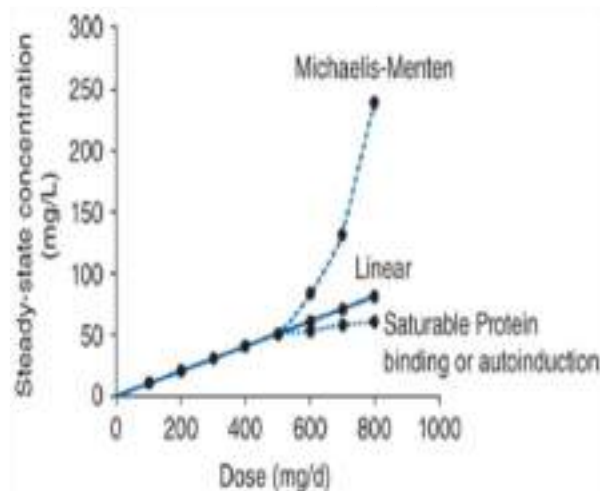


**Clearance (CL)**

- Definition: clearance (Cl) is the volume of serum or blood completely cleared of the drug per unit of time. Thus, the dimension of clearance is the volume per unit of time, such as **L/h or mL/min**.

> What is the benefit of Clearance?
>
> To calculate the maintenance dose

- The liver is most often the organ responsible for drug metabolism
- Clearance is a descriptive term used to evaluate the efficiency of drug removal from the body
- Clearance is not an indicator of how much drug is being removed it only represents the theoretical volume of blood that is cleared of drug per unit of time
- Because clearance is a first-order process the amount of drug removed depends on the concentration
- Clearance (CL) is computed by taking the ratio of the dose and area under the serum concentration/time curve (AUC) for a drug that is administered intravenously

$$CL=Dose/AUC$$

If the dose is administered extra vascularly the bioavailability fraction (must be included to compensate for a drug that does not reach the systemic vascular system:

$$CL= (FD)/ AUC$$

From the previous equation we can calculate the volume of distribution (V) using the area under the serum concentration/time curve (AUC):

$$V=D/ (K_e * AUC)$$

> The benefit of $K_e$ is to calculate the time interval

Where $K_e$ is the elimination rate constant. For doses administered extra vascularly, the bioavailability fraction (F) must be included to compensate for a drug that does not reach the systemic vascular system:

$$V=(FD)/ (K_e * AUC)$$

Clearance can be thought of as the proportionality constant that makes the average steady-state drug level equal/proportional to the rate of drug administration

Clearance (rate out) can be calculated from the dose (maintenance dose) (rate in) and average steady-state concentration:

$$Cl=MD/Css$$

> *This equation of Clearance is used for individualized patients.*

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 (Css):

$$MD=Css.Cl$$

Since the concentration of the chemical in its volume of distribution is most commonly sampled by analysis of blood or plasma, clearances are most commonly described as the plasma clearance or blood clearance of a substance.

**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:

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

LBF is liver blood flow, $f_B$ is the fraction of unbound drug in the blood, **Cl´ is intrinsic clearance**

For drugs with a low hepatic extraction ratio, hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance:

$$Cl= f_B. Cl'_{int}.$$

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 (drug-protein complexes are far too big to exit 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 the liver or cardiac disease Examples of drugs with low hepatic extraction ratios include valproic acid, phenytoin, and warfarin.

For drugs with a high hepatic extraction ratio, 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. Examples of drugs with high hepatic extraction ratios include lidocaine, morphine, and most tricyclic antidepressants.

**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 (Clsec), and the fraction of drug reabsorbed in the kidney (FR):

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

1. $V = dose/conc.$
2. $V = Cl/K_e$
3. $V = V_B + \dfrac{f_B}{f_T} V_T$

**The volume of distribution:**

The volume of distribution (V) is a term that relates the measured concentration (Cp) at a time to the mass of the drug (at that time This term is defined as the **apparent volume of distribution (V)**

> The benefit of Volume of distribution to calculate loading dose

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 the volume of distribution is in volume units, such as L or mL

At any given time after the drug has been absorbed from extravascular sites, the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) depends on the amount of drug in the body ($A_B$) and the volume of distribution

$$C = A_B/V.$$

($A_B$=Amount of the drug in the body. V=Volume of distribution)

The large volume of distribution indicates that the drug distributes extensively into body tissues and fluids

If the volume of distribution (V) is known for a patient, it is possible to administer a loading dose (LD) that will attain a specified steady-state drug concentration Css.

$$LD = Css \cdot V$$

The volume of distribution can be very small if the drug is primarily contained in the blood (warfarin V 57 L), or very large if the drug distributes widely in the body and is mostly bound to bodily tissues (digoxin V 500 L)

The physiologic determinates of the 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 determinant of the drug's distribution volume. for example, the reason warfarin has such a small volume of distribution is that it is highly bound to serum albumin so the free fraction of the 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 the free fraction of drug in the tissues

$f_T$ unbound drug concentration in the tissue/total tissue drug concentration)

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 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 a plasma protein binding drug interaction occurs 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 $f_B$ resulting in an increased volume of distribution

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

We can calculate the volume of distribution (V) using the area under the serum concentration/time curve (AUC):

$$V = D / (K_e \cdot AUC)$$

Where $K_e$ is the rate elimination rate constant. For doses administration extravascularly, the bioavailability fraction (F) must be included to compensate for a drug that does not reach the systemic vascular system:

$$V = (FD) / (K_e \cdot AUC)$$

**Half-life and elimination rate constant:**

When drugs that follow, linear pharmacokinetics are given to humans, serum concentrations decline in a curvilinear fashion (Figure 5). 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 (Figure 6). 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 5.** 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.
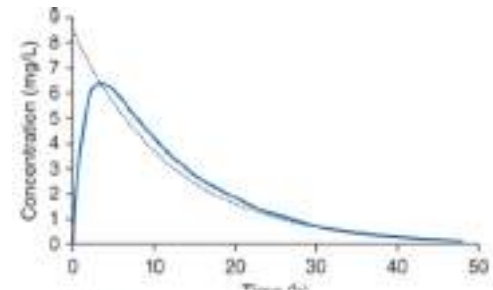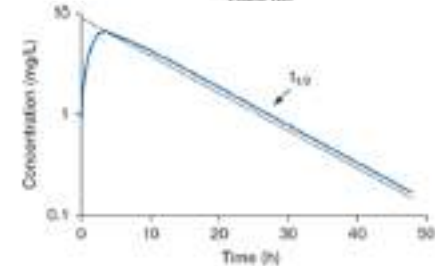


**Figure 6.** Data from Figure 3 is plotted on semilogarithmic axes. Serum concentrations decline in a straight line in both cases.



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**.).

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 (AB):

$$\textbf{Elimination rate = AB} \cdot \textbf{k}_e$$

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:

$$\textbf{t}_{1/2} = \textbf{0.693/k}_e$$

The elimination rate constant can also be measured graphically by computing the slope of the log concentration versus the time graph during the elimination phase:

$$\textbf{k}_e = -\textbf{(ln C1} - \textbf{ln C2)/ (t}_1 - \textbf{t}_2\textbf{)}$$

> When $k_e$ is high → Rate of elimination is high
>
> The benefit of $k_e$ is to determine Time interval

Half-life is important because it determines the **time required to reach a steady state** and **the dosage interval**. It takes approximately 3 to 5 half-lives to reach steady-state concentrations during continuous dosing.

Half-life is also used to determine the dosage interval for a drug. For example, it may be desirable to maintain maximum steady-state concentrations at 20 mg/L and minimum steady-state concentrations at 10 mg/L. In this case, it would be necessary to administer the drug every half-life because the minimum desirable concentration is one-half the maximum desirable concentration.

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

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

The half-life and elimination rate constant for a drug can change either because of a change in clearance or a change in the volume of distribution.

Because the values for clearance and volume of distribution depend solely on physiological parameters and can vary independently of each other, they are known as **independent parameters**.

## Bioavailability:

When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. **The fraction of the administered drug that is delivered to the systemic circulation is known as the bioavailability** or can be defined as the rate and the extent to which the active ingredients or active moiety is absorbed from a drug product and become available at the site of action

The bioavailability (would be computed by dividing the area under the curve after oral administration AUCpo by the AUC after intravenous administration AUCi.v.

$$F = AUC_{po}/AUC_{iv}$$



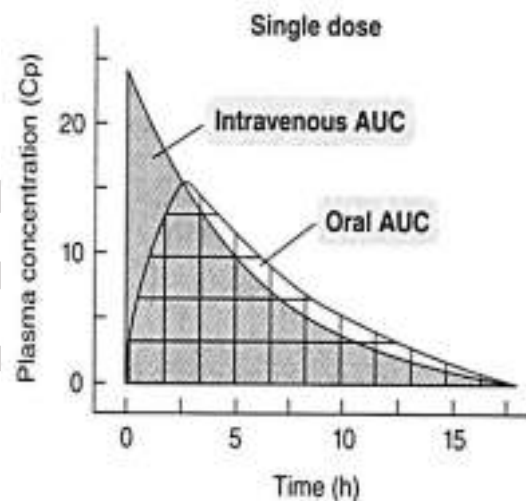**Figure 7.** The area under the serum concentration/time curve (**AUC**).

If it is not possible to administer the same dose intravenously and extravascularly because poor absorption or presystemic metabolism yields serum concentrations that are too low to measure, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration.
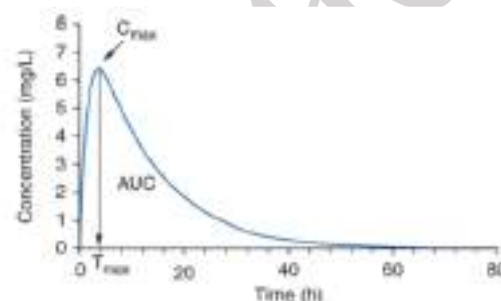
$$F = (AUC_{PO}/AUC_{IV}) (D_{IV}/D_{PO})$$

## Bioequivalence

The absence of significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

Concentration/time curves are superimposable when the area under the total serum concentration/time curve (AUC), maximum concentration (Cmax), and time that the maximum concentration occurs (Tmax) are identical within statistical limits (Figure 8).



**Figure 8.** Area under the serum concentration/time curve (AUC), the maximum concentration ($C_{max}$), and the time that the maximum concentration occurs ($T_{max}$).

The ratio of the area under the serum concentration/time curves for the generic (AUC $_{generic}$) and brand one (AUC $_{brand}$) drug dosage forms is known as *the relative bioavailability* (since the reference AUC is derived from the brand name drug dosage form.

$$F_{relative} = AUC_{generic}/AUC_{\underline{brand}}$$

The United States Food and Drug Administration ( has defined bioequivalence as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study The ratio of the area under the serum concentration/time curves for the generic (AUC generic) and brand name ( drug dosage forms is known as the relative bioavailability (F) since the reference AUC is derived from the brand name drug dosage form

## The area under the curve (AUC)

The area under the plasma drug concentration-time curve (reflects the actual body exposure to the drug after administration of a dose of the drug and is expressed in mg*h/L This area under the curve is dependent on the rate of elimination of the drug from the body and the dose administered

The AUC is directly proportional to the dose when the Drug follows linear kinetics

The AUC is inversely proportional to the clearance of the drug That is, the higher the clearance, the less time the drug spends in systemic circulation and the faster the decline in the plasma drug concentration Therefore, in such situations the body's exposure to the drug and the area under the concentration-time curve is smaller.

$$AUC = Dose / Cl$$

$$Cl = Dose / AUC$$
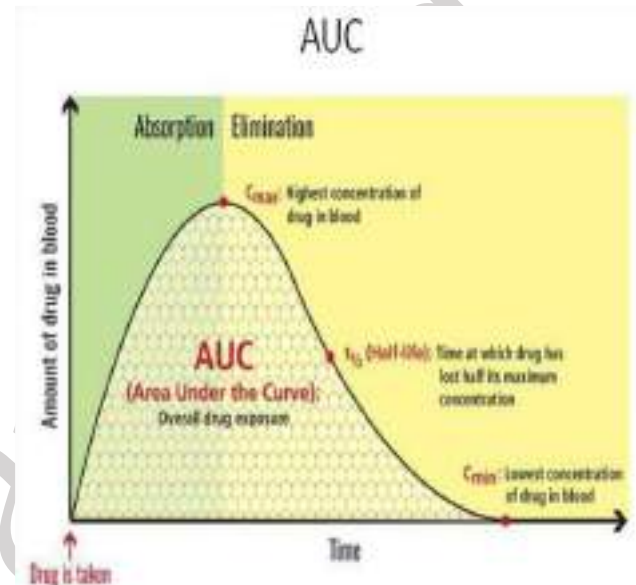


**Figure 7.** The area under the curve (AUC)

| Pharmacokinetic Parameter | Abbreviation | Fundamental Units | Units Example |
|---|---|---|---|
| Area under the curve | AUC | Concentration × time | µg × hr/mL |
| Total body clearance | $Cl_T$ | Volume/time | L/hr |
| Renal clearance | $Cl_R$ | Volume/time | L/hr |
| Hepatic clearance | $Cl_H$ | Volume/time | L/hr |
| Apparent volume of distribution | $V_D$ | Volume | L |
| Volume of distribution at steady state | $V_{ss}$ | Volume | L |
| Peak plasma drug concentration | $C_{max}$ | Concentration | mg/L |
| Plasma drug concentration | $C_p$ | Concentration | mg/L |
| Steady-state drug concentration | $C_{ss}$ or $C_{av}$ | Concentration | mg/L |
| Time for peak drug concentration | $T_{max}$ | Time | hr |
| Dose | $D_0$ | Mass | mg |
| Loading dose | $D_L$ | Mass | mg |
| Maintenance dose | $D_M$ | Mass | mg |
| Amount of drug in the body | $D_B$ | Mass | mg |
| Rate of drug infusion | R | Mass/time | mg/hr |
| First-order rate constant for drug absorption | $k_A$ | 1/time | 1/hr or hr⁻¹ |
| Zero-order rate constant for drug absorption | $k_0$ | Mass/time | mg/hr |
| First-order rate constant for drug elimination | k (sometimes referred to as kel) | 1/time | 1/hr or hr⁻¹ |
| Elimination half-life | $t_½$ | Time | hr |
| Fraction of drug absorbed | F | (no units) | Ranges from 0 to 1 (0%–100%) |

# Clinical Pharmacokinetic Equations and Calculations

## One-compartment model equations for linear pharmacokinetics:

### ❖ Intravenous Bolus Equation

- Used when: -

A- A drug is given as an intravenous bolus, which distributes from the blood into the tissues quickly.

B-A short infusion of 5–30 minutes can avoid these types of adverse effects, and if the intravenous infusion time is very short compared to the half-life of the drug so that a large amount of the drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

C-If the drug given by I.V infusion and distribution is not rapid, it is still possible to use a one-compartment model intravenous bolus equation if the duration of the distribution phase and infusion time is small compared to the half-life of the drug and only a small amount of drug is eliminated during the infusion and distribution phases.

- In this case, a one-compartment model intravenous bolus equation can be used:

$$C = (D/V)e^{-k_e t}$$

Where t is the time after the intravenous bolus was given (t = 0 at the time the dose was administered), C is the concentration at time = t, V is the volume of distribution, and $k_e$ is the elimination rate constant.

- $V = D/C_0$……………. or $V = D/ [C_0 − C_{predose}]$, if not first dose

- $C_0 = C/e^{-ket}$

- $k_e = − (\ln C1 − \ln C2) / (t1 − t2)$

For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20 minutes. Because the patient received theophylline during previous hospitalizations, it is known that the volume of distribution is 30 L, the elimination rate constant equals $0.115 \ h^{-1}$, and the half-life ($t_{1/2}$) is ($t_{1/2} = 0.693/k_e = 0.693/0.115 \ h^{-1} = 6 \ h$). To compute the expected theophylline concentration 4 hours after the dose was given, a one-compartment model intravenous bolus equation can be used:

$C = (D/V) \ e^{-ket} = (400 \ mg/30L) \ e^{- (0.115 \ h-1) \ (4 \ h)} = 8.4 \ mg/L.$

Pharmacokinetic parameters for patients can also be computed for use in the equations. If two or more serum concentrations are obtained after an intravenous bolus dose, the elimination rate constant, half-life, and volume of distribution can be calculated.

For example, a patient was given an **intravenous loading dose of phenobarbital 600 mg** over a period of about **an hour**. **One** day and **four** days after the dose was administered phenobarbital serum concentrations were **12.6** mg/L and **7.5** mg/L, respectively.
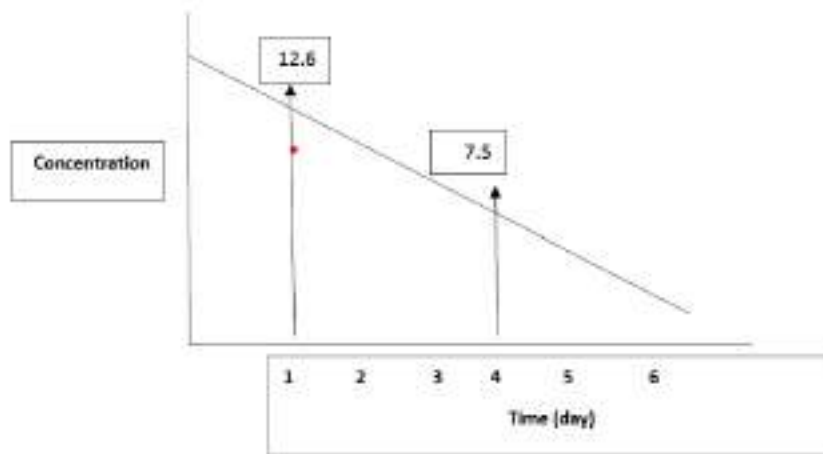


1- The elimination rate constant can be computed using the following equation:

$$k_e = - (\ln C1 - \ln C2)/ (t_1 - t_2),$$

Where t1 and C1 are the first time/concentration pair and t2 and C2 are the second time/concentration pair;

$Ke = - [\ln (12.6$ mg/L$) - \ln (7.5$ mg/L$)]/ (1$ d$- 4$d$) =$ **0.173 d$^{-1}$**.

2-The elimination rate constant can be converted into the half-life using the following equation:
$t_{1/2} = 0.693/0.173$ d$^{-1} =$ **4 d**.

3- The serum concentration at time = zero (C0) ( the initial concentration )can be computed using a variation of the intravenous bolus equation: **C0 = C/e$^{-ket}$**,

Where t and C are a time/concentration pair that occurs after the intravenous bolus dose.

Either phenobarbital concentration can be used to compute C0. In this case, the time/concentration pair on day 1 will be used (time 1=d, concentration = 12.6 mg/L): C0 = C/e$^{-ket}$ = (12.6 mg/L)/e$-(0.173$ d$^{-1}$) (1 d) = **15.0 mg/L**.

The volume of distribution (V) is then computed by dividing the **dose** by the serum concentration at time = 0.

**V = D/C0** = 600 mg/ (15 mg/L) = **40 L**.

## ❖ Continuous and Intermittent Intravenous Infusion Equations

Some drugs are administered using a continuous intravenous infusion, and if the infusion is discontinued the serum concentration/time profile decreases in a straight line when graphed on semi-logarithmic axes.
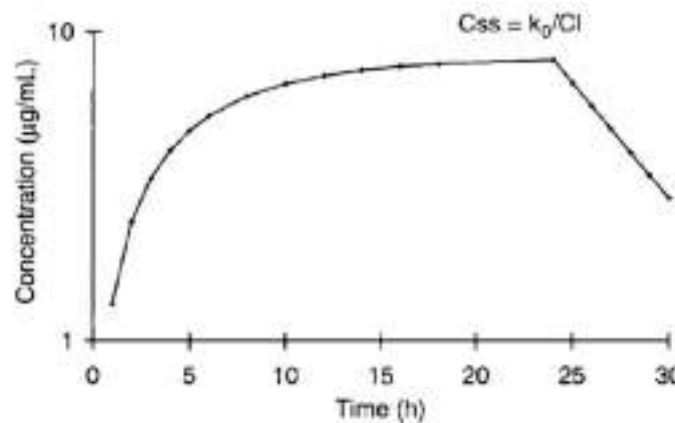


We can calculate the concentration at any time depending on whether the infusion is running or stopped or we are in a study state or not.

A- while the infusion is running:

$$C = (k_0/Cl)(1 - e^{-k_e t}) = [k_0/(k_e V)](1 - e^{-k_e t})$$

Cl: drug clearance

$k_0$: drug infusion rate (mg/h or μg /min)

Cl: drug clearance, $Cl = k_e V$

$K_e$: elimination rate constant

t: the time that the infusion has been running.

$$Css = K_0 /Cl$$

$$Css = K_0 /K_e V$$

B- If the infusion is allowed to continue until a steady state- is achieved

The steady-state concentration (Css) can be calculated easily:

$$Css = k_0 / Cl = k_0 / (k_e V)$$

C- If the infusion is stopped

If the infusion is stopped, postinfusion serum concentrations (**C postinfusion**) can be computed by calculating the concentration when the infusion ended (**C end**) by the following equation

$$C_{postinfusion} = C_{end}e^{-k_e t_{postinfusion}}$$

ke is the elimination rate constant

$t_{postinfusion}$ is the postinfusion time ($t_{postinfusion} = 0$ at end of infusion and increases from that point)

For example, a patient is administered 60 mg/h of theophylline. It is known from previous hospital admissions that the patient has the following pharmacokinetic parameters for theophylline: V = 40 L and ke = 0.139 h$^{-1}$.

1. Calculate the serum concentration of theophylline in this patient **after receiving the drug for 8 hours** and at **SteadyState**:

   **For 8 hours mean that the infusion is running**

$\mathbf{C= [k_0/(k_e V)]\ (1 - e^{-k_e t})}$ = [(60 mg/h)/ (0.139 h$^{-1}$ · 40 L)](1 − e$^{- (0.139\ h−1)\ (8\ h))}$ = 7.2 mg/L;

   **At SteadyState**:

Css = $k_0$/ ($k_e$V) = (60 mg/h)/ (0.139 h$^{-1}$ • 40 L) = 10.8 mg/L.

2. Calculate the theophylline serum concentration at 6 hours after the infusion stopped would be:

   $\mathbf{C_{postinfusion} = C_{end}\ e^{-k_e t}}$ postinfusion

= (7.2 mg/L) e$^{- (0.139\ h−1)\ (6\ h)}$ = 3.1 mg/L.



3. Calculate the theophylline serum concentration If the infusion ran until SteadyState was achieved, the serum concentration 6 hours after the infusion ended would be:

   $\mathbf{C_{postinfusion} = C_{end}\ e^{-k_e t}}$ postinfusion =(10.8 mg/L) e$^{-(0.139\ h−1)(6\ h)}$ = 4.7 mg/L.
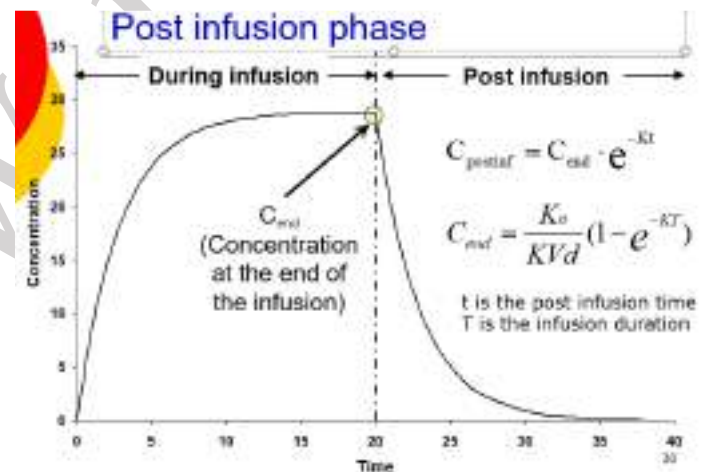
## The elimination rate constant

$k_e = -(\ln C1 - \ln C2)/ (t_1 - t_2)$

The volume of distribution (V): can be computed using the following equations

**1-At steady state and when we know $C_0$**

$$\mathbf{V= Dose\ /\ C0\quad or\quad V= Cl/K_e}$$

**2- in I.V infusion or before steady state**

$$V = \frac{k_0(1 - e^{-k_e t'})}{k_e[C_{max} - (C_{predose}e^{-k_e t'})]}$$

**C $_{predose}$ = used only if we have multiple doses and we have predose concentration but when we are in the first dose or C $_{predose}$ not given in the question → C $_{predose}$= zero**

### ❖ Extravascular Equation

When a drug is administered extravascularly (e.g., orally intramuscularly, subcutaneously, transdermally, etc.), absorption into the systemic vascular system must take place. If serum concentrations decrease in a straight line when plotted on semi-logarithmic axes after drug absorption is complete, a one-compartment model extravascular equation can be used to describe the serum concentration/time curve

$$C = \frac{Fk_a D}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t})$$

where t is the time after the extravascular dose was given (t = 0 at the time the dose was administered), C is the concentration at time = t, F is the bioavailability fraction, $k_a$ is the absorption rate constant, D is the dose, V is the volume of distribution, and $k_e$ is the elimination rate constant.

• The absorption rate constant describes how quickly the drug is absorbed with a large number indicating fast absorption and a small number indicating slow absorption.

• If the serum concentration/time curve displays a distribution phase, it is still possible to use one-compartment model equations after an extravascular dose is administered. In order to do this, serum concentrations are obtained only in the post-distribution phase.

• Since the absorption rate constant is also hard to measure in patients, it is also desirable to avoid drawing drug serum concentrations during the absorption phase in clinical situations.
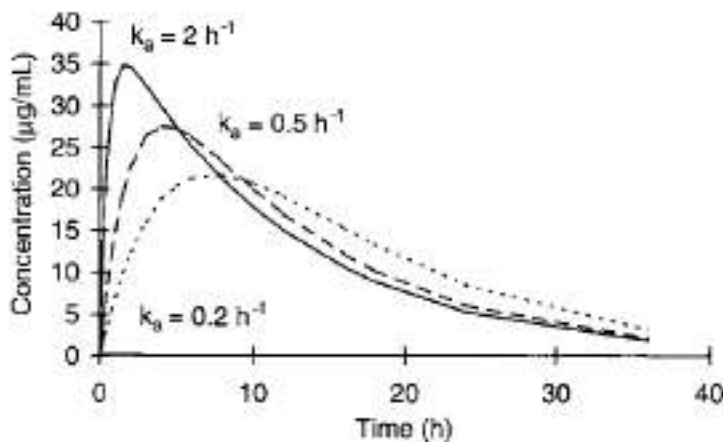
FIGURE (3) - Serum concentration/time curves for extravascular drug administration for agents following one-compartment pharmacokinetics. The absorption rate constant (ka) controls how quickly the drug enters the body. A large absorption rate constant allows the drug to enter the body quickly while a small elimination rate constant permits the drug to enter the body more slowly. The solid line shows the concentration/time curve on semi-logarithmic axes for an elimination rate constant equal to 2 h−1. The dashed and dotted lines depict serum concentration/time plots for elimination rate constants of 0.5 h−1 and 0.2 h−1, respectively.

After the end of the absorption phase the C can be calculated by the equation of I.V bolus

$$C = (D/V)e^{-k_e t}$$

### The hybrid volume of distribution/bioavailability (V/F) parameter

Since the volume of distribution relate the dose given with the obtained concentration and since in the extravascular route not all the dose enter the bloodstream so we use (V/F) to indicate the value of the volume of distribution

**V/F = D/C$_0$……………. or**

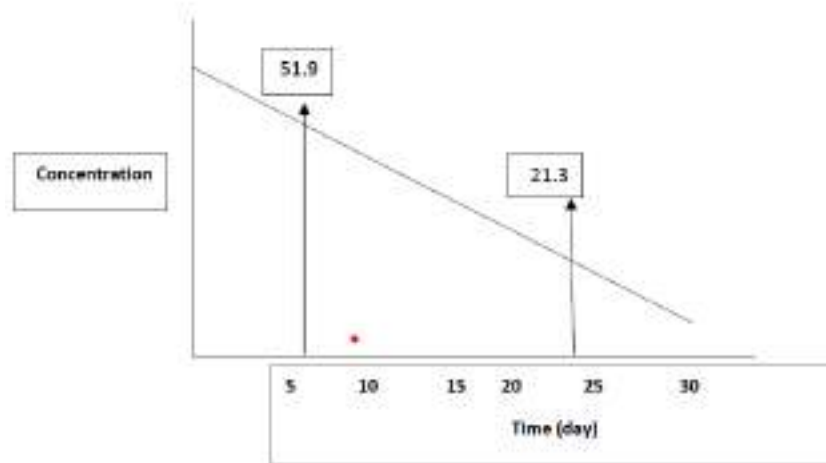**V = D/ [C$_0$ − C$_{predose}$], if not first dose**

**C0 = C/e$^{-ket}$**                 **Ke = − (ln C1 − ln C2) / (t$_1$ − t$_2$)**

For example, a patient is given an oral dose of valproic acid 750 mg in capsules. Six and twenty-four hours after the dose, the valproic acid serum concentrations are 51.9 mg/L and 21.3 mg/L, respectively. Calculate pharmacokinetic parameters.



The elimination rate constant ($k_e$) is computed using the following relationship:

$$k_e = - (\ln C1 - \ln C2) / (t_1 - t_2),$$

where C1 is the first concentration at time = $t_1$, and C2 is the second concentration at time = $t_2$;

$$k_e = - [\ln (51.9 \text{ mg/L}) - \ln (21.3 \text{ mg/L})]/ (6 \text{ h} - 24 \text{ h}) = 0.0495 \text{ h}^{-1}.$$

The elimination rate constant can be translated into the half-life using the following equation:

$$t_{1/2} = 0.693/k_e = 0.693/0.0495 \text{ h}^{-1} = 14 \text{ h}.$$

The hybrid constant volume of distribution/bioavailability (V/F) is computed by taking the quotient of the dose and the extrapolated serum concentration at time = 0.

The extrapolated serum concentration at time = zero ($C_0$) is calculated using a variation of the intravenous bolus equation: $C_0 = C/e^{-ket}$, where t and C are a time/concentration pair that occurs after administration of the extravascular dose in the post absorption and post distribution phases. Either valproic acid concentration can be used to compute C0. In this situation, the time/concentration pair at 24 hours will be used (time = 24 hours, concentration= 21.3mg/L):

$$C_0 = C/e^{-ket} = (21.3 \text{ mg/L}) / e^{- (0.0495 \text{ h}-1) (24 \text{ h})} = 70 \text{ mg/L}.$$

The hybrid volume of distribution/bioavailability constant (V/F) is then computed:

$$V/F = D/C_0 = 750 \text{ mg/ } (70 \text{ mg/L}) = 10.7 \text{ L}.$$

### ❖ Multiple-Dose and Steady-State Equations

In most cases, medications are administered to patients as multiple doses, and drug serum concentrations for therapeutic drug monitoring are not obtained until a steady state is achieved. For these reasons, multiple-dose equations that reflect steady-state conditions are usually more useful in clinical settings than single-dose equations.

In order to change a single-dose equation to the multiple-dose version, it is necessary to multiply each exponential term in the equation by the multiple-dosing factors:

$$(1 - e^{-nk_i\tau})/(1 - e^{-k_i\tau})$$

Where **n** is the number of doses administered, $k_i$ is the rate constant found in the exponential of the single dose equation, and **τ** is the dosage interval.

Example: the equation for multiple doses of intermittent IV will be: (Table 2-1)

$$C = [k_0/(k_eV)](1 - e^{-k_et'})\,[(1 - e^{-nk_e\tau})/(1 - e^{-k_e\tau})]$$

### Multiple-Dose at steady state

The number of doses (**n**) is large, the exponential term in the numerator of the multiple dosing factor ($-nk_i\tau$) becomes a large negative number, and the exponent approaches zero. Therefore, the steady-state version of the multiple dosing factor becomes the following: **$1/(1 - e^{-k_i\tau})$**, where $k_i$ is the rate constant found in the exponential of the single dose equation and **τ** is the dosage interval.

🞤 **n** is ↑ → $nk_i\tau$ ) will be large negative number → $e^{-nk_i\tau}$ approaches zero
  The state version of the multiple dosing factors becomes
Example: the equation for multiple dose of IV bolus at steady state will be :( table 2-1)

$$C = (D/V)[e^{-k_et}/(1 - e^{-k_e\tau})]$$

❖ **Average Steady-State Concentration Equation**

$$Css = [F(D/\tau)]/Cl$$

where F is the bioavailability fraction, D is the dose, $\tau$ is the dosage interval, and Cl is the drug clearance.

***This equation works for any single or multiple-compartment model (model-independent equation).***

The average steady-state concentration equation is very useful when the half-life of the drug is long compared to the dosage interval or if a sustained-release dosage form is used.

If an average steady-state concentration (Css) is known for a drug, the hybrid pharmacokinetic constant clearance/bioavailability (Cl/F) can be computed:

$$Cl/F = (D/\tau)/Css$$

# Designing individualized dosage regimens using one-compartment model equations

• The goal of therapeutic drug monitoring is to customize medication doses that provide optimal drug efficacy without adverse reactions.

• **Note: $\tau$ should be rounded to the nearest 6, 8, 12, 18, 24, 36, 48, etc hours**.

• Example: a patient with simple partial seizures that needs to receive valproic acid capsules (V = 12 L, $k_e$ = 0.05 h$^{-1}$, $T_{max}$ = 3 h, F = 1.0) and maintain steady-state maximum ($C_{ssmax}$) and minimum ($C_{ssmin}$) concentrations of 80 mg/L and 50 mg/L, respectively:

$\tau$ = [(ln $C_{ssmax}$ − ln $C_{ssmin}$)/$k_e$] + $T_{max}$ = [(ln 80 mg/L − ln 50 mg/L) / 0.05 h$^{-1}$] + 3 h = **12.4 h, round to practical dosage interval of 12 h**

D = [($C_{ssmax}$V)/F] [(1 − e$^{-ke\tau}$)/e$^{-keTmax}$] = [(80 mg/L · 12 L)/1.0)][(1 − e$^{(-0.05\ h-1)(12\ h)}$)/ e$^{(-0.05\ h-1)(3\ h)}$] = 503 mg, round to practical dose of 500 mg. **The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.**

❖ **Michaelis -Menten equations for saturable pharmacokinetics**

When the dose of a drug is increased and steady-state serum concentrations do not increase in a proportional fashion, but instead increase more than expected

$$D = (V_{max} \cdot Css)/(Km + Css)$$

• Where D is the dose,

• Css is the steady-state drug concentration,

• $V_{max}$ is the maximum rate of drug metabolism, and

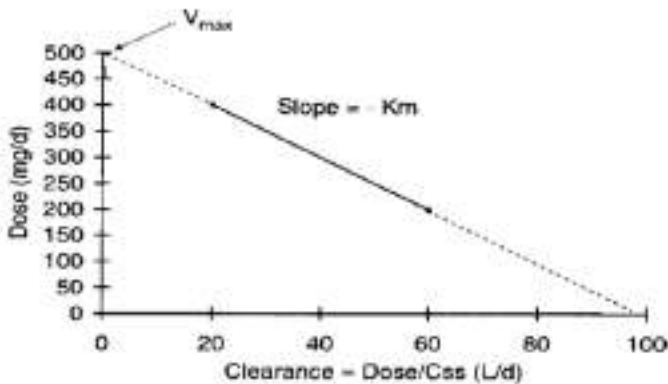• Km is the concentration where the rate of metabolism equal $V_{max}/2$.

**Figure**: relation between dosing rate and the clearance in Michaelis -Menten pharmacokinetics

• Form of the equation of a straight line

$$y = y_{intercept} + [(slope)\ x]$$

• The Michaelis Menten equation is rearranged to the following formula

$$D = Vmax - [Km\ (D/Css)]\ ......\ (1)$$

$$Vmax = (the\ y_{intercept})$$

$$Km = (the\ slope) = -(y\ 1 - y\ 2)\ /\ (x1 - x\ 2)$$

$$Km = [(Dose\ 1 - Dose\ 2)]\ /\ [(D\ 1\ /Css\ 1) - (D\ 2\ /Css\ 2)]\ .....\ (2)$$

$$Vmax = D + [Km\ (D/Css)]\ ......\ (3)$$

Note in question you get 2 doses of the drug and 2 Css and will be asked to calculate the actual pharmacokinetics parameters (Km, $V_{max}$) and use of this actual pharmacokinetic parameter to calculate a new dose to answer the question

1. Calculate actual Km using eq. (2)

2. Substitute the actual km value in eq. (3) to calculate actual Vmax

3. You can use the values of actual Vmax and Km to measure new Css from different dose by eq. (1)

• An example is a patient receiving phenytoin for the treatment of tonic-clonic seizures. The patient received a dose of 300 mg/d with a Steady-State concentration of 8 mg/L and a dose of 500 mg/d with a Steady-State concentration equal to 22 mg/L

• The dose/Steady-State concentration ratios are 37.5 L/d and 22.7 L/d for the first and second doses, respectively ([300 mg/d]/ 8 mg/L = 37.5 L/d; [500 mg/d]/22 mg/L= 22.7 L/d). A plot of this data yields a Vmax 807 mg/d and a Km 13.5 mg/L.

• The phenytoin dose to reach a SteadyState concentration equal to 13 mg/L is

D = ($V_{max}$. Css) / (Km + Css)

D= 807 mg/d 13 mg/L)/ (13.5 mg/L +13 mg/L) **396 mg/d**, rounded to a practical dose of **400 mg/d.**

Ex. OP is a 28-year-old, 55-kg female with complex partial seizures. She has the following information available: Css = 8 mg/L while receiving phenytoin 300 mg at bedtime and Css = 22 mg/L while receiving phenytoin 400 mg at bedtime. Compute the patient's Michaelis-Menten parameters for phenytoin and the phenytoin dose that would achieve Css = 15 mg/L.

Km= [(Dose 1 - Dose 2)] / [(D 1 /Css 1) - (D 2 /Css 2)]

Km= [300-400] / [(300/8)m- (400/22)]

= -100 / [37.5 – 18.18]

Km = 100/19.32 = 5.2 mg/L Css

Vmax= D + [Km (D/Css)]

= 300 + {5.2/(300/8)} = 495 mg/d

D= (Vmax. Css) / [Km + Css)]

= (495* 15) / (5.2+ 15) = **369.5mg**

TABLE 2-1 Single-Dose, Multiple-Dose, and Steady-State One-Compartment Model Equations

| ROUTE OF ADMINISTRATION | SINGLE DOSE | MULTIPLE DOSE | STEADY STATE |
|---|---|---|---|
| Intravenous bolus | $C = (D/V)e^{-k_e t}$ | $C = (D/V)e^{-k_e t}[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$ | $C = (D/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$ |
| Continuous intravenous infusion | $C = [k_0/(k_e V)](1 - e^{-k_e t})$ | N/A | $Css = k_0/Cl = k_0/(k_e V)$ |
| Intermittent intravenous infusion | $C = [k_0/(k_e V)](1 - e^{-k_e t'})$ | $C = [k_0/(k_e V)](1 - e^{-k_e t'})[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$ | $C = [k_0/(k_e V)][(1 - e^{-k_e t'})/(1 - e^{-k_e \tau})]$ |
| Extravascular (postabsorption, postdistribution) | $C = [(FD)/V]e^{-k_e t}$ | $C = [(FD)/V]e^{-k_e t}[(1 - e^{-nk_e \tau})/(1 - e^{-k_e \tau})]$ | $C = (FD/V)[e^{-k_e t}/(1 - e^{-k_e \tau})]$ |
| Average steady-state concentration (any route of administration) | N/A | N/A | $Css = [F(D/\tau)]/Cl$ |

Symbol key: C is drug serum concentration at time = t, D is dose, V is volume of distribution, $k_e$ is the elimination rate constant, n is the number of administered doses, $\tau$ is the dosage interval, $k_0$ is the infusion rate, Cl is clearance, t' is infusion time, N/A is not applicable.

**Table 2.2. Single Dose, Multiple Dose, and Steady State Pharmacokinetic Constant Computations Utilizing a One Compartment Model.**

| ROUTE OF ADMINISTRATION | SINGLE DOSE | MULTIPLE DOSE | STEADY STATE |
|---|---|---|---|
| Intravenous bolus | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V = D/C_0$ <br> $Cl = k_e V$ | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V = D/(C_0 - C_{predose})$ <br> $Cl = k_e V$ | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V = D/(C_0 - C_{predose})$ <br> $Cl = k_e V$ |
| Continuous intravenous infusion | N/A | N/A | $Cl = k_0/Css$ |
| Intermittent intravenous infusion | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V = [k_0(1 - e^{-k_e t'})]/[k_e[C_{max} - (C_{predose}e^{-k_e t'})]]$ <br> $Cl = k_e V$ | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V = [k_0(1 - e^{-k_e t'})]/[k_e[C_{max} - (C_{predose}e^{-k_e t'})]]$ <br> $Cl = k_e V$ | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V = [k_0(1 - e^{-k_e t'})]/[k_e[C_{max} - (C_{predose}e^{-k_e t'})]]$ <br> $Cl = k_e V$ |
| Extravascular (postabsorption, postdistribution) | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V/F = D/C_0$ <br> $Cl/F = k_e(V/F)$ | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V/F = D/(C_0 - C_{predose})$ <br> $Cl/F = k_e(V/F)$ | $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ <br> $t_{1/2} = 0.693/k_e$ <br> $V/F = D/(C_0 - C_{predose})$ <br> $Cl/F = k_e(V/F)$ |
| Average steady-state concentration (any route of administration) | N/A | N/A | $Cl/F = (D/t)/Css$ |

**Key Symbols**

| | | | |
|---|---|---|---|
| C1 | drug serum concentration at time = t1 | Cl | Drug clearance |
| C2 | drug serum concentration at time = t2 | Cl/F | the hybrid constant clearance/bioavailability fraction |
| Ke | is the elimination rate constant | Cpredose | the predose concentration |
| t1/2 | the half-life | Css | steady-state concentration |
| V | the volume of distribution | N/A | Not applicable |
| K0 | continuous infusion rate | D | Dose |
| t' | is the infusion time | C0 | Concentration at time = 0 |
| V/F | hybrid constant volume of distribution/bioavailability fraction | | |

**Table 2-3 Equations to Compute Individualized Dosage Regimens for Various Routes of Administration**

| ROUTE OF ADMINISTRATION | DOSAGE INTERVAL ($\tau$), MAINTENANCE DOSE (D OR $k_0$), AND LOADING DOSE (LD) EQUATIONS |
|---|---|
| Intravenous bolus | $\tau = (\ln Css_{max} - \ln Css_{min})/k_e$ <br> $D = Css_{max} V(1 - e^{-k_e\tau})$ <br> $LD = Css_{max} V$ |
| Continuous intravenous infusion | $k_0 = Css\ Cl = Css\ k_e V$ <br> $LD = CssV$ |
| Intermittent intravenous infusion | $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + t'$ <br> $k_0 = Css_{max} k_e V[(1 - e^{-k_e\tau})/(1 - e^{-k_e t'})]$ <br> $LD = k_0/(1 - e^{-k_e\tau})$ |
| Extravascular (postabsorption, postdistribution) | $\tau = [(\ln Css_{max} - \ln Css_{min})/k_e] + T_{max}$ <br> $D = [(Css_{max}V)/F][(1 - e^{-k_e\tau})/e^{-k_e T_{max}}]$ <br> $LD = (Css_{max}V)/F$ |
| Average steady-state concentration (any route of administration) | $D = (Css\ Cl\ \tau)/F = (Css\ k_e V\tau)/F$ <br> $LD = (CssV)/F$ |

**Symbol key:**

$Css_{max}$ and $Css_{min}$ are the maximum and minimum steady-state concentrations

Ke = is the elimination rate constant,

V = is the volume of distribution,

Css = is the steady state concentration,

$k_0$ = is the continuous infusion rate,

t´ = is the infusion time,

$T_{max}$ = is the time that $Css_{max}$ occurs,

F is the bioavailability fraction

# *Drug dosing in special population*

• Renal or hepatic disease will decrease the elimination or metabolism of the majority drugs and change the clearance of the agent.

• Dialysis procedures, conducted using artificial kidneys in patients with renal failure, remove some medications from the body while the pharmacokinetics of other drugs are not changed.

• Heart failure results in low cardiac output which decreases blood flow to eliminating organs, and the clearance rate of drugs with moderate-to-high extraction ratios are particularly sensitive to alterations in organ Blood flow.

• Obesity adds excessive adipose tissue to the body which may change the way drugs distribute in the body and alter the volume of distribution for the medication.

• Drug interactions can inhibit or induce drug metabolism, alter drug-protein binding, or change blood flow to organs that eliminate or metabolize the drug.

# **Renal Disease**

The equation that describes these various routes of renal elimination is:

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

• fB is the free fraction of drug in the blood,

• GFR is glomerular filtration rate

• RBF is renal blood flow,

• Cl′sec is the intrinsic clearance for tubular secretion of unbound drug,

• FR is the fraction reabsorbed.

**1-Measurement of glomerular filtration rate:**

Glomerular filtration rate (GFR) can be estimated using the modified Modification of Diet in Renal Disease (MDRD) equation:

**GFR (in mL/min / 1.73 m$^2$)** = $186 \cdot SCr^{-1.154} \cdot Age^{-0.203} \cdot$ X (0.742, if female) and X (1.21, if African-American).

- X 0.742 mean the female have 74% of GFR in blood
- Normal value of SCr is 0.7-1.2, if its ↑ → problem at renal function → ↓ GFR, because ↓ renal function

**For example,** the estimated GFR for a 53-year-old African-American male with a SCr = 2.7 mg/dL would be computed as follows: GFR = $186 \cdot (2.7 \text{ mg/dL})^{-1.154} \cdot (53 \text{ y})^{-0.203} \cdot 1.21 = 32$ mL/min / 1.73 m².

## Measurement and Estimation of Creatinine Clearance

## Method 1: -

$$\text{CrCl (in mL/min)} = (UCr \cdot Vurine) / (SCr \cdot T),$$

o Where UCr is the urine creatinine concentration in mg/dL, Vurine is the volume of urine collected in mL, SCr is the serum creatinine collected at the midpoint of the urine collection in mg/dL, and T is the time in minutes of the urine collection.

Method 1 is the most appropriate method, because of its collection between UCr & SCr, while another method used only SCr.

o Because creatinine renal secretion exhibits diurnal variation, most nephrologists use a 24-hour urine collection period for the determination of creatinine clearance.

o For example, 24-hour urine was collected for a patient with the following results: UCr = 55 mg/dL, Vurine = 1000 mL, SCr = 1.0 mg/dL, T = 24 h × 60 min/h = 1440 min, and

CrCl (in mL/min) = (UCr · Vurine) / (SCr · T) =

(55 mg/dL · 1000 mL) / (1.0 mg/dL · 1440 min) = 38 mL/min.

## Method 2:

**Cockcroft and Gault**: The Cockcroft-Gault method should only be used in patients:

*A - ≥18 years old*

*B-Actual weight within 30% of their ideal body weight.* (**Not obese**)

To detect the obesity patient by equation:

**% overweight = TBW – IBW/IBW X 100**

*C- Stable serum creatinine concentrations.*

*For male …**CrCl = [(140 − age) BW]/ (72 · SCr)**

*For females…**CrCl= [0.85(140 − age) BW] / (72 · SCr)**

Where CrCl is estimated creatinine clearance in mL/min, age is in years, BW is body weight in kg, and SCr is serum creatinine in mg/dL.

• The **0.85 correction factor** for females is present because women have smaller muscle mass than men, producing less creatinine per day.

IBW (in kg) = 50 + 2.3(Ht − 60) for male or

IBW (in kg) = 45 + 2.3(Ht − 60), for female

| |
|---|
| **5 feet = 60 inch.** |
| **1 inch. = 2.54 cm** |
| **1 feet = 12 inch.** |

• Where Ht is height in **inches**,

• For example, a 55-year-old, 80-kg, 5-ft 11-in male has
a serum creatinine equal to 1.9 mg/dL. The estimated creatinine clearance would be:

IBW males= 50 + 2.3 (Ht − 60) = 50 + 2.3(71 − 60) = 75 kg,

So the patient is within 30% of his ideal body weight and the Cockcroft-Gault method can be used;

CrCl= [(140 -age) BW]/ (72 · SCr) = [(140 − 55 y) 80 kg] / (72 · 1.9 mg/dL) = 50 mL/min.

**Method 3:**

**Jelliffe and Jelliffe method:** Used if serum creatinine values are not stable

**1-First step** in this method is to estimate creatinine production. The formula for this is different for males and females due to gender-dependent differences in muscle mass:

**Ess male = IBW [29.3 − (0.203 · age)]**

**Ess female = IBW [25.1 − (0.175 · age)]**

Where **Ess** is the excretion of creatinine, **IBW** is ideal body weight in kilograms, and age is in years.

**2-Step2**: correct creatinine production for renal function

**Ess corrected = Ess [1.035 − (0.0337 · Scrave)]**

| |
|---|
| **SCr$_{average}$ = SCr 1 +SCr2/2** |

**3-Step3:** adjust the estimated creatinine clearance value according to whether the renal function is getting better or worse

$$E = Ess_{corrected} - \frac{[4\,IBW(Scr_2 - Scr_1)]}{\Delta t}$$

**4-Step4:** calculate CrCl

**CrCl (in mL/min / 1.73m$^2$) = E/ (14.4 · Scrave)**

Where **Scrave** is the average of the two serum creatinine determinations in mg/dL, Scr1 is the first serum creatinine and Scr2 is the second serum creatinine both in mg/dL, and **Δt** is the time that expired between the measurement of Scr1 and Scr2 in **minutes**.

**Method 4:**

**Salazar and Corcoran**

*A-If patients are not within 30% of their ideal body weight (**obese**)*

*B-≥18 years old*

*C- Stable serum creatinine concentrations*

$$CrCl_{est(males)} = \frac{(137 - age)[(0.285 \cdot Wt) + (12.1 \cdot Ht^2)]}{(51 \cdot S_{Cr})}$$

$$CrCl_{est(females)} = \frac{(146 - age)[(0.287 \cdot Wt) + (9.74 \cdot Ht^2)]}{(60 \cdot S_{Cr})}$$

Where **age** is in years, **Wt**. is weight in kg, **Ht** is height in <u>**m**</u>, and **SCr** is serum creatinine in mg/dL.

**Method 5:**

**Methods to estimate creatinine clearance for children and young adults or children**:

1- Age 0–1 year,

$$\text{CrCl}_{est} \text{ (in mL/min / 1.73 m}^2) = (0.45 \cdot Ht) / SCr$$

2-Age 1–20 years,

$$\text{CrCl}_{est} \text{ (in mL/min / 1.73 m}^2) = (0.55 \cdot Ht)/SCr$$

o Where **Ht** is in <u>**cm**</u> and **SCr** is in mg/dL.

**Q/ What are the best way to correct the dose of a drug eliminated mainly by kidney if renal impairment occurred A-decrease the dose without any change in time interval or B-increase the time interval without any change in a dose?**

*Answer:*

B- Increase the time interval without any change in a dose since this way produce concentration time profile similar to that of healthy patient.
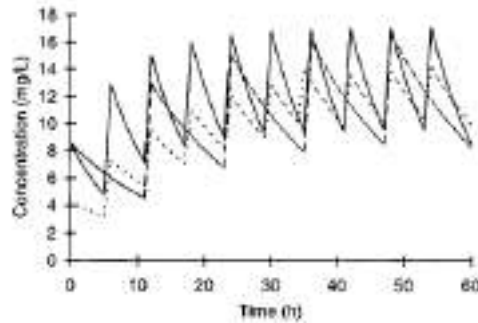
**FIGURE 1:** Serum concentration versus time profile for a patient with normal kidney function receiving a really eliminated drug at the dose of 300 mg every 6 hours (solid line). In a patient with renal dysfunction, it is possible to give the same dose and prolong the dosage interval (300 mg every 12 hours, dashed line), or a reduced dose at the same dosage interval (150 mg every 6 hours, dotted line). Giving the same dose at a longer dosage interval in a patient with renal disease usually results in a concentration/time profile similar to that seen in a normal patient receiving the normal dose. However, giving a smaller dose and keeping the dosage interval the same usually produces a concentration/time profile with a lower peak steady-state concentration and a higher trough steady-state concentration.

## The relationship between drug clearance or $K_e$ and creatinine clearance: -

The relationship between drug clearance and creatinine clearance is usually approximated by a straight line with a slope that is a function of the renal clearance for the drug and an intercept that is related to the non-renal clearance of the drug.

**A-For digoxin,** an equation that describes the relationship between digoxin clearance (Cl) and creatinine clearance (CrCl in mL/min) is:

$$Cl \text{ (in mL/min)} = 1.303 \cdot CrCl + ClNR$$

where **ClNR** is non-renal clearance and equals **20 mL/min** in patients with moderate-severe heart failure and **40 mL/min** in patients with no or mild heart failure.
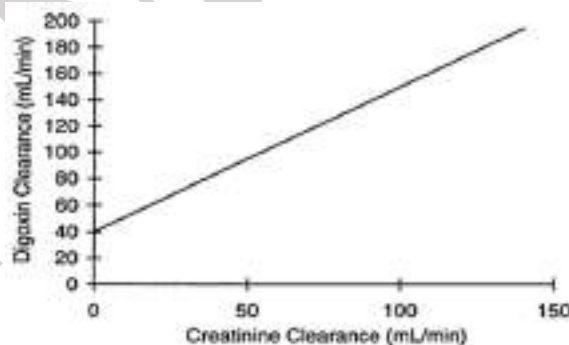


**FIGURE 2:** Relationship between creatinine clearance and digoxin clearance used to estimate initial digoxin clearance when no drug concentrations are available. The Y- axis intercept (40mL/min) is non-renal clearance for digoxin in patients with no or mild heart failure. If the patient has moderate to severe heart failure, non-renal clearance is set to a value of 20mL/min.

**Elimination rate constant ($k_e$)** can also be estimated using creatinine clearance, but it is a dependent pharmacokinetic parameter whose result is reliant on the relative values of clearance and volume of distribution ($k_e = Cl/V$).

❖ Because of this, changes in the elimination rate constant may not always be due to changes in the renal elimination of the drug.

❖ For the aminoglycoside antibiotics, an equation that represents the relationship between aminoglycoside antibiotic elimination rate constant (ke) and creatinine clearance (CrCl in mL/min) is:

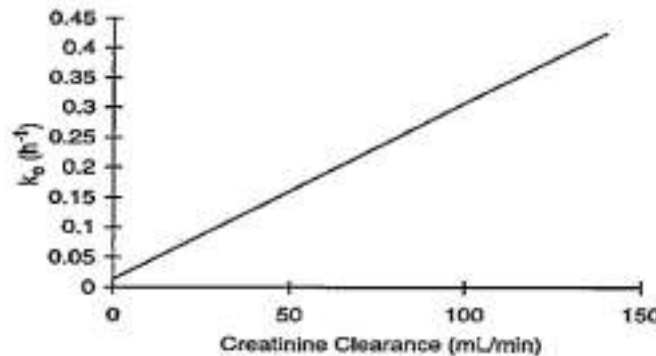$$K_e \text{ (in h}^{-1}) = 0.00293 \cdot CrCl + 0.014$$



**FIGURE 3:** Relationship between creatinine clearance and aminoglycoside elimination rate constant (ke) used to estimate initial aminoglycoside elimination when no drug concentrations are available. The y-axis intercept ($0.014 h^{-1}$) is non renal elimination for aminoglycosides.

❖ **Volume of distribution in decreased renal function**

Volume of distribution can also change in patients with decreased renal function.

**A-** The volume of distribution of drugs can increase in patients with poor kidney function If Plasma protein binding displacement of drug occur by endogenous or exogenous substances that would normally be eliminated by the kidney but accumulate in the blood of patients with poor kidney function.

**B-** The volume of distribution of a drug can decrease if compounds normally excreted by the kidney accumulate to the extent that displacement of drug from tissue binding sites occurs.

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

**C-** Digoxin volume of distribution decreases in patients with decreased renal function according to the following equation:

$$V \text{ (in L)} = 226 + [(298 \cdot CrCl)/ (29.1 + CrCl)]$$

Where CrCl is in mL/min. The decline in volume of distribution presumably occurs because of displacement of tissue-bound digoxin.

# Hepatic Disease

o Unfortunately, there is no single laboratory test that can be used to assess liver function in the same way that measured or estimated creatinine clearance is used to measure renal function.

The most common way to estimate the ability of the liver to metabolize drug is to determine the **Child-Pugh score** for a patient.

### Determination of Child-Pugh Scores

> Child-Pugh Scores is used to assess the prognosis of chronic liver disease mainly cirrhosis.

The Child-Pugh score consists of five laboratory tests or clinical symptoms. The five areas are serum albumin, total bilirubin, prothrombin time, ascites, and hepatic encephalopathy.

Each of these areas is given a score of 1 (normal)–3 (severely abnormal; Table 3-2), and the scores for the five areas are summed.

The Child-Pugh score for a patient with normal liver function is 5 while the score for a patient with grossly abnormal serum albumin, total bilirubin, and prothrombin time values in addition to severe ascites and hepatic encephalopathy is 15.

**TABLE 3-2 Child-Pugh Scores for Patients with Liver Disease[27]**

| TEST/SYMPTOM | SCORE 1 POINT | SCORE 2 POINTS | SCORE 3 POINTS |
|---|---|---|---|
| Total bilirubin (mg/dL) | <2.0 | 2.0–3.0 | >3.0 |
| Serum albumin (g/dL) | >3.5 | 2.8–3.5 | <2.8 |
| Prothrombin time (seconds prolonged over control) | <4 | 4–6 | >6 |
| Ascites | Absent | Slight | Moderate |
| Hepatic encephalopathy | None | Moderate | Severe |

## Hepatic Clearance: -

Liver blood flow averages 1–1.5 L/min in adults with about one-third coming from the hepatic artery and about two-thirds coming from the portal vein. Orally administered medications must pass through the liver before entering the systemic circulation, so if the drug is metabolized by the liver, a portion of the dose may be inactivated by the hepatic first-pass effect before having a chance to exert a pharmacologic effect. In addition to hepatic metabolism, drugs can be eliminated unchanged by the liver in the bile. The equation that describes hepatic drug metabolism is

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

Where LBF is liver blood flow, $f_B$ is the fraction of unbound drug in the blood, and $Cl'_{int}$ is intrinsic clearance.

❖ There are two major types of liver disease: hepatitis and cirrhosis.

❖ Patients with acute hepatitis usually experience mild, transient decreases in drug metabolism that require no or minor changes in drug dosing.

❖ If the patient develops chronic hepatitis, it is likely that irreversible hepatocyte damage will be more widespread, and drug dosage changes will be required at some point.

❖ In patients with hepatic cirrhosis, there is a permanent loss of functional hepatocytes so drug dosage schedules usually need to be modified.

❖ When hepatocytes are damaged, they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduce the hepatic clearance of the drug. If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and **bioavailability will increase.**

❖ A simultaneous decrease in hepatic clearance and liver first-pass effect results in extremely **large increases in steady-state concentrations** for orally administered drugs.

❖ Liver blood flow also decreases in patients with cirrhosis because hepatocytes are replaced by nonfunctional connective tissue which increases intraorgan pressure causing portal vein hypertension and shunting of blood flow around the liver.

❖ The decrease in liver blood flow results in less drug delivery to still-functioning hepatocytes and depresses hepatic drug clearance even further.

• The liver produces albumin and, probably, α1-acid glycoprotein, the two major proteins that bind acidic and basic drugs, respectively, in the blood.

❖ In patients with cirrhosis, the production of these proteins declines. When this is the case, the free fraction of drugs in the blood increases because of a lack of binding proteins.

❖ Additionally, high concentrations of endogenous substances in the blood that are normally eliminated by the liver, such as bilirubin, can displace drugs from plasma protein binding sites.

❖ The increased free fraction in the blood will alter hepatic and renal drug clearance as well as the volume of distribution for drugs that are highly protein bound

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

❖ Since clearance typically decreases and volume of distribution usually increases or does not appreciably change for a drug in patients with liver disease, the elimination rate constant ($k_e$) almost always decreases in patients with decreased liver function

$$(K_e = Cl/V)$$

**Implications of Hepatic Disease on Serum Drug Concentration Monitoring and Drug Effects**

The pharmacokinetic alterations that occur with hepatic disease result in complex changes for total and unbound steady-state concentrations and drug response. The changes that occur depend on whether the drug has a low or high hepatic extraction ratio. As previously discussed, hepatic drug metabolism is described by the following equation:

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

**1-For drugs with a low hepatic extraction ratio (≤30%)**

The numeric value of liver blood flow is much greater than the product of the unbound fraction of drug in the blood and the intrinsic clearance of the compound (LBF >>fB· Cl'$_{int}$), and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow and the sum in the denominator of the hepatic clearance equation is almost equal to liver blood flow [LBF ≈ LBF + (f$_B$ · Cl'$_{int}$)]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to the product of free fraction in the blood and the intrinsic clearance of the drug for a drug with a low hepatic extraction ratio:

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

**2-For drugs with a high hepatic extraction ratio (≥70%)**

For drugs with a high hepatic extraction ratio (≥70%), the numeric value of liver blood flow is much less than the product of unbound fraction of drug in the blood and the intrinsic clearance of the agent (LBF<<fB·Cl'int), and the sum in the denominator of the hepatic clearance equation is almost equal to the product of free fraction of drug in the blood and intrinsic clearance [fB·Cl'int≈LBF+(fB·Cl'$_{int}$)]. When this substitution is made into the hepatic clearance equation, hepatic clearance is equal to liver blood flow for a drug with a high hepatic extraction ratio:

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

**3-For drugs with intermediate hepatic extraction ratios**

For drugs with intermediate hepatic extraction ratios, the entire liver clearance equation must be used and all three factors, liver blood flow, free fraction of drug in the blood, and intrinsic clearance are important parameters that must be taken into account. An extremely important point

for clinicians to understand is that the factors which are important determinants of hepatic clearance are different depending on the liver extraction ratio for the drug.

**Answering the question of drug interaction**

The equation used to answer the questions

**1- The hepatic clearance**

The hepatic clearance of drugs with low hepatic extraction ratios equals to the product of free fraction in the blood and intrinsic clearance

$$(Cl_H = f_B.Cl'_{int}).$$

While hepatic clearance of drugs with high hepatic extraction ratios equals to liver blood flow only.

$$(Cl_H = LBF).$$

**2- Volume of distribution**

$$(V = V_B + [f_B/f_T]V_T)$$

**3-Half-life:**

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

**4- Steady-state concentration:** Affected by bioavailability (F) and clearance (CL)

$$Css = [F(D/\tau)]/Cl$$

**5-The unbound steady-state concentration** of the drug in the blood equals the product of the total steady-state concentration and the unbound fraction of the drug in the blood

$$Css_u = f_B Css$$

**6-The effect of the drug:** -increases when the unbound steady-state concentration increases and decreases when Cssu declines.

**7-Bioavailability (F): -**When hepatocytes are damaged, they are no longer able to metabolize drugs efficiently, and intrinsic clearance decreases which reduce the hepatic clearance of the drug. If the drug experiences a hepatic first-pass effect, less drug will be lost by presystemic metabolism and bioavailability will increase.

So, bioavailability used only for oral drugs and inversely proportional with LBF, $F_B$, $CL_{int}$

**e.g.: For answering**

**1-You have to know if the drug is low or high extraction ratio in order determine what the factors that effect on CL. are**

**2-You have to know what is/ are the parameter(s) that changed according to the given question and what are the effect of this change in the factors according to the equations from 1 to 7 .**

# Drug interactions

**Plasma Protein–Binding Displacement Drug Interactions**

*A-For a drug with a low hepatic extraction ratio*, plasma protein–binding displacement drug interactions cause major pharmacokinetic alterations, but these interactions are not clinically significant because the pharmacologic effect of the drug does not change (see figure 4 below)



Source: Larry A. Bauer: Applied Clinical Pharmacokinetics, 3rd Edition
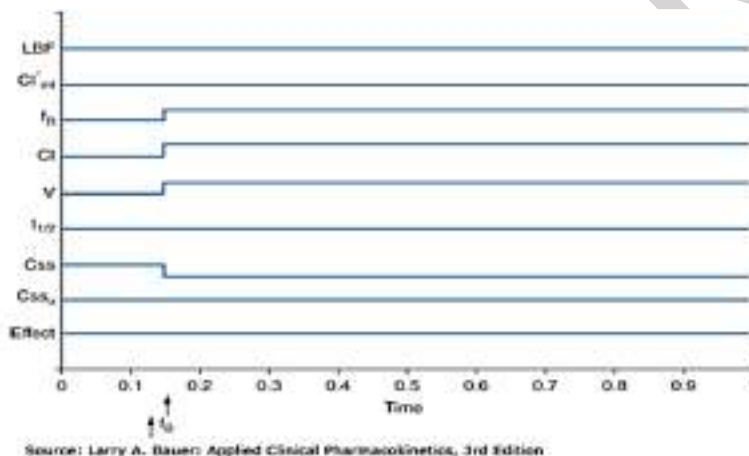
*Because the clearance of the drug is dependent on the fraction of unbound drug in the blood and intrinsic clearance for a low hepatic extraction ratio agent*, the addition of a plasma protein–binding displacing compound will increase clearance ($\uparrow Cl = \uparrow f_B Cl'_{int}$) and volume of distribution ($\uparrow V = VB + [\uparrow f_B/f_T]VT$).

Because half-life depends on clearance and volume of distribution, it is likely that because both increase, half-life will not substantially change ($t_{1/2} = [0.693 \cdot \uparrow V]/\uparrow Cl$).

However, it is possible that if either clearance or volume of distribution changes disproportionately, half-life will change.

The total Steady-State concentration will decline because of the increase in clearance ($\downarrow Css = k_0/\uparrow Cl$, where $k_0$ is the infusion rate of the drug). However, the unbound Steady-State concentration will remain unaltered because the free fraction of the drug in the blood is higher than it was before the drug interaction occurred ($Cssu = \uparrow fB \downarrow Css$).

The pharmacologic effect of the drug does not change because the free concentration of the drug in the blood is unchanged. An example of this drug interaction is the addition of diflunisal to patients stabilized on warfarin therapy.

Diflunisal displaces warfarin from plasma protein–binding sites but does not augment the anticoagulant effect of warfarin.

*B- For drugs with high hepatic extraction ratios* given intravenously, plasma protein–binding displacement drug interactions cause both major pharmacokinetic and pharmacodynamics changes (see Figure 5).
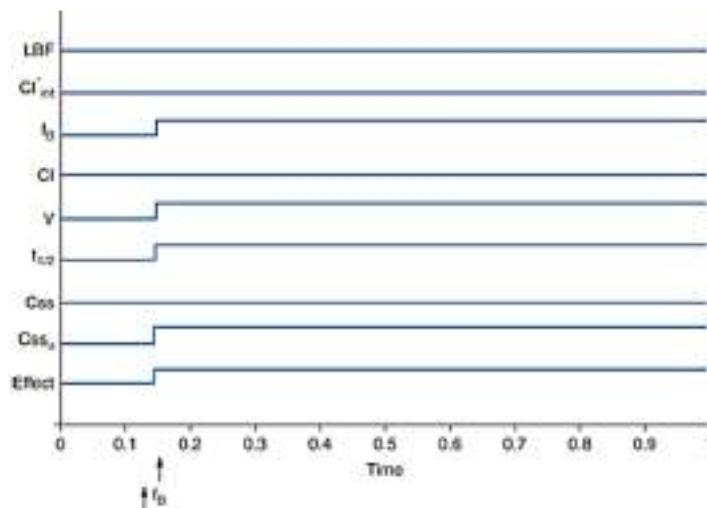


Because the clearance of the drug is dependent solely on liver blood flow for an agent of this type, total clearance does not change.

However, both the volume of distribution [$\uparrow V = V_B + (\uparrow f_B/f_T) V_T$] and half-life [$\uparrow t_{1/2} = (0.693 \cdot \uparrow V)/Cl$] will increase because of the plasma protein–binding displacement of the drug.

Because total clearance did not change, the total Steady-State concentration remains unaltered. However, the free concentration ($\uparrow Cssu = \uparrow f_B \cdot Css$) and pharmacologic effect ($\uparrow effect \propto \uparrow Cssu$) of the drug will both increase.

If available, unbound drug concentration could be used to document the drug interaction. If a drug with a high hepatic extraction ratio is given orally, a plasma protein–binding displacement drug interaction will cause a simultaneous increase in the unbound fraction of the drug in the blood ($\uparrow f_B$) and the hepatic presystemic metabolism of the drug. Hepatic presystemic metabolism increases because the higher unbound fraction of drugs in the blood allows more drug molecules to enter the liver where they are ultimately metabolized. The increase in hepatic presystemic metabolism leads to an increased first-pass effect and decreased drug bioavailability ($\downarrow F$).

Total Steady-State drug concentrations will be lower because of decreased drug bioavailability [$\downarrow Css = (\downarrow F [D/t])/Cl$].

However, the unbound Steady-State drug concentration and pharmacologic effect remain unchanged due to this type of drug interaction because the increase in the unbound fraction is offset by the decrease in the total SteadyState concentration ($\sim$Cssu = $\uparrow$fB$\downarrow$Css).

## Inhibition Drug Interactions

Inhibition of hepatic drug metabolism is probably the most common drug interaction encountered in patients. For drugs with low hepatic extraction ratios, this type of drug interaction produces clinically significant changes in drug pharmacokinetics and effect. FIGURE 6
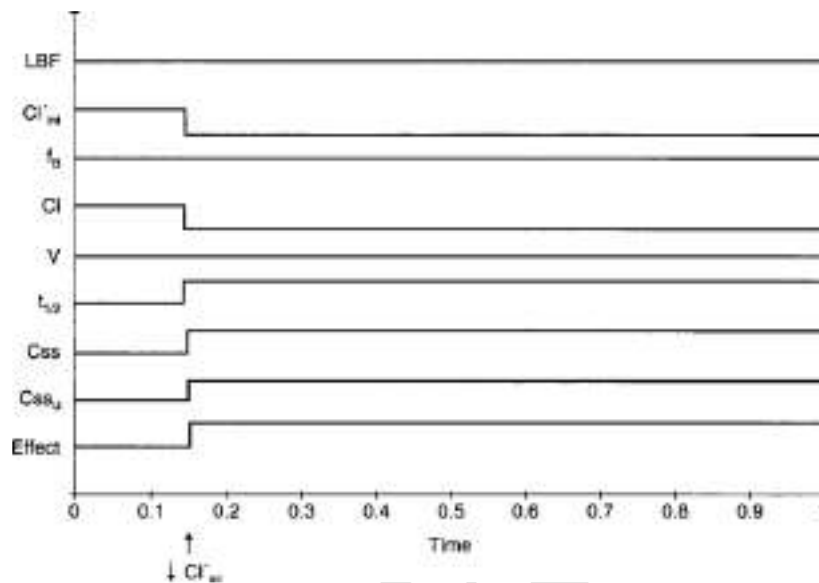


**FIGURE 6:** Changes in physiologic parameters (LBF = liver blood flow, Cl'int = intrinsic clearance, fB = free fraction of drug in the blood), pharmacokinetic parameters (Cl = clearance, V = volume of distribution, $t_{1/2}$ = half-life), and drug concentration and effect (Css = total steady-state concentration; Cssu = unbound steady-state concentration; effect = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance decreases (indicated by arrow). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

The addition of a hepatic enzyme inhibitor will decrease the intrinsic clearance and total clearance for the drug ($\downarrow$Cl = $f_B\downarrow$Cl'$_{int}$). Because the volume of distribution remains unaltered, the half-life of the drug will increase ($\uparrow t_{1/2}$ = [0.693 • V]/$\downarrow$Cl).

As a result of the total clearance decrease, total Steady-State drug concentrations will increase ($\uparrow$Css = $k_0$/$\downarrow$Cl).

The rise in unbound Steady-State drug concentration will mirror that seen with total drug concentration, and the effect of the drug will increase in proportion to unbound concentration.

An example of this drug interaction is the addition of ciprofloxacin to a patient stabilized on theophylline therapy.

For drugs with high hepatic extraction ratios, this category of drug interaction produces variable effects depending on the route of administration for the drug. If the drug is given intravenously and an enzyme inhibitor is added, the decrease in intrinsic clearance is usually not substantial

enough to cause major pharmacokinetic and pharmacodynamics effects because clearance is a function of liver blood flow FIGURE 7
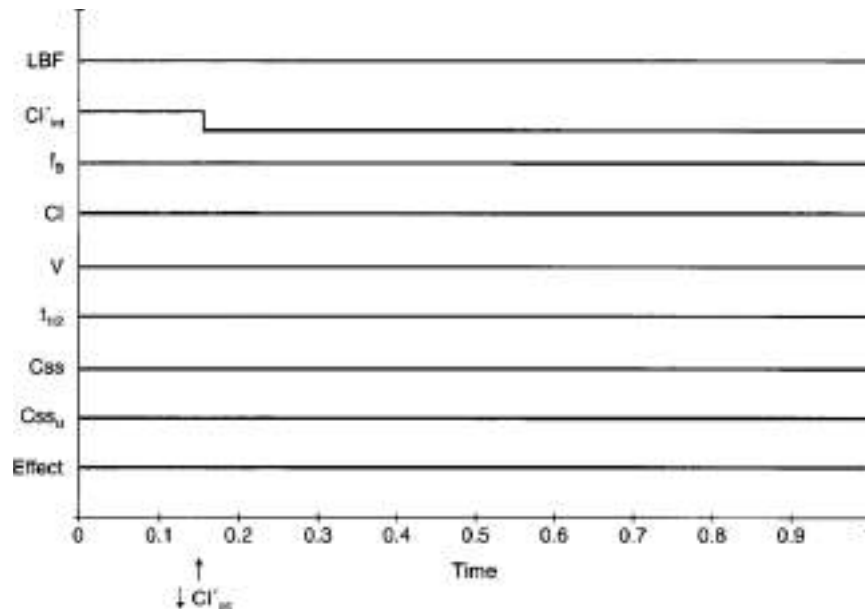


**FIGURE 7** Changes in physiologic parameters (LBF = liver blood flow, Cl′int = intrinsic clearance, fB = free fraction of drug in the blood), pharmacokinetic parameters (Cl = clearance, V = volume of distribution, t1/2 = half-life), and drug concentration and effect (Css = total steady-state concentration; Cssu = unbound steady-state concentration; effect = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance decreases (indicated by arrow). A uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could decrease due to loss of functional hepatocytes secondary to liver cirrhosis or a drug interaction that inhibits drug-metabolizing enzymes.

However, if the drug is given orally and an enzyme inhibitor is added to therapy, the presystemic metabolism of the medication may be greatly depressed and the first-pass effect can decrease dramatically leading to improved drug bioavailability.

This effective increase in administered oral dose will increase the total and unbound steady-state drug concentrations, and lead to an increase in the pharmacologic effect of the drug.

### Induction Drug Interactions

Drugs with **low hepatic extraction ratios** exhibit clinically significant drug interactions that alter drug pharmacokinetics and pharmacologic response when hepatic enzyme inducers are coadministered. **FIGURE 8**
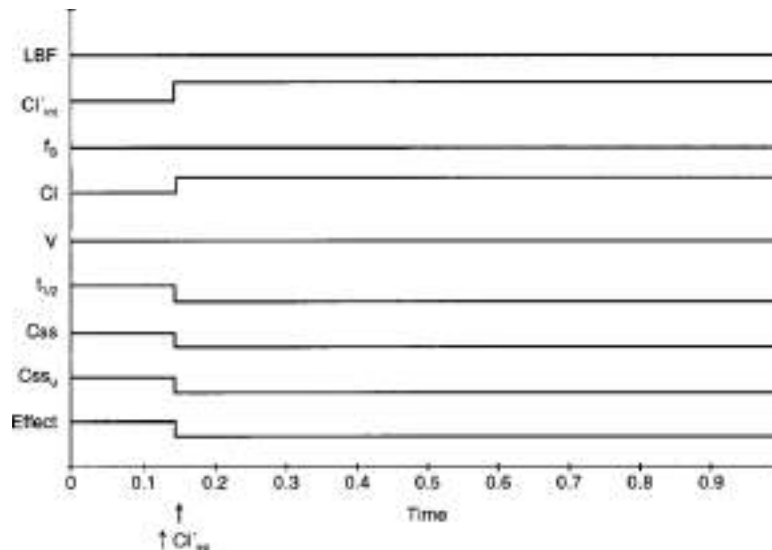


**FIGURE 8** Changes in physiologic parameters (LBF = liver blood flow, Cl′int = intrinsic clearance, fB = free fraction of drug in the blood), pharmacokinetic parameters (Cl = clearance, V =volume of distribution, t1/2 = half-life), and drug concentration and effect (Css = total steady-state concentration; Cssu = unbound steady-state concentration; effect = pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance increases (indicated by arrow). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

Enzyme inducers increase the intrinsic clearance of the drug and thereby increase the total clearance of the medication ($\uparrow Cl = f_B \uparrow Cl'_{int}$). The increase in total clearance will cause a shorter half-life as the volume of distribution remains unchanged ($\downarrow t_{1/2} = [0.693 \cdot V]/\uparrow Cl$).

Increased total clearance will also cause decreased total SteadyState concentration ($\downarrow Css = k_0/\uparrow Cl$), unbound Steady-State concentration ($\downarrow Cssu = f_B \downarrow Css$), and pharmacologic effect ($\downarrow effect \propto \downarrow Cssu$).

Carbamazepine is a potent enzyme inducer that, when added to a patient's therapy, can cause this type of drug interaction with many other medications such as warfarin. **FIGURE 8**

Changes in physiologic parameters (LBF, liver blood flow; Cl′int, intrinsic clearance; fB, free fraction of drug in the blood), pharmacokinetic parameters (Cl, clearance; V, volume of distribution; t1/2, half-life), and drug concentration and effect (Css, total Steady-State concentration; Cssu, unbound SteadyState concentration effect, pharmacologic effect) for a low hepatic extraction ratio drug if intrinsic clearance increases. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

**For drugs with high hepatic extraction ratios**, this type of drug interaction results in variable effects depending on the route of administration for the drug.

If the drug is given intravenously and an enzyme inducer is added, the increase in intrinsic clearance is usually not large enough to cause major pharmacokinetic and pharmacologic effect alterations because total clearance is a function of liver blood flow. FIGURE 9
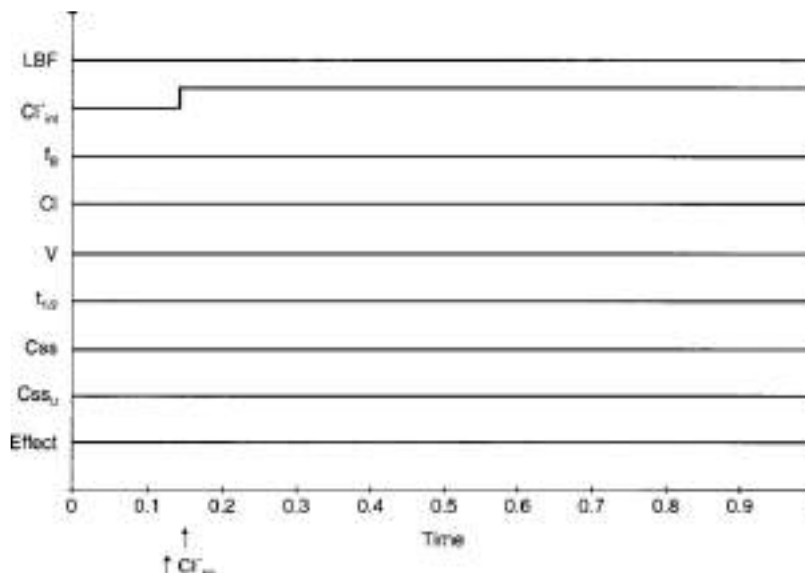


**FIGURE 9** Changes in physiologic parameters (LBF = liver blood flow, Cl′int = intrinsic clearance, fB = free fraction of drug in the blood), pharmacokinetic parameters (Cl = clearance, V = volume of distribution, t1/2 = half-life), and drug concentration and effect (Css = total steadystate concentration; Cssu = unbound steady-state concentration; effect = pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance increases (indicated by arrow). An uptick in the line indicates an increase in the value of the parameter, while a downtick in the line indicates a decrease in the value of the parameter. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.

However, if the drug is given orally and an enzyme inducer is added to the treatment regimen, presystemic metabolism of the medication may be increased and the first-pass effect augmented leading to decreased drug bioavailability. This effective decrease in administered oral dose will decrease the total and unbound steady-state drug concentrations and lead to a decrease in the pharmacologic effect of the agent.

Changes in physiologic parameters (LBF, liver blood flow; $Cl'_{int}$, intrinsic clearance; $f_B$, free fraction of drug in the blood), pharmacokinetic parameters (Cl, clearance; V, volume of distribution; $t_{1/2}$, half-life),

and drug concentration and effect (Css, total steady-state concentration; Cssu, unbound steady-state concentration; effect, pharmacologic effect) for a high hepatic extraction ratio drug if intrinsic clearance increases. Intrinsic clearance could increase due to a drug interaction that induces drug-metabolizing enzymes.