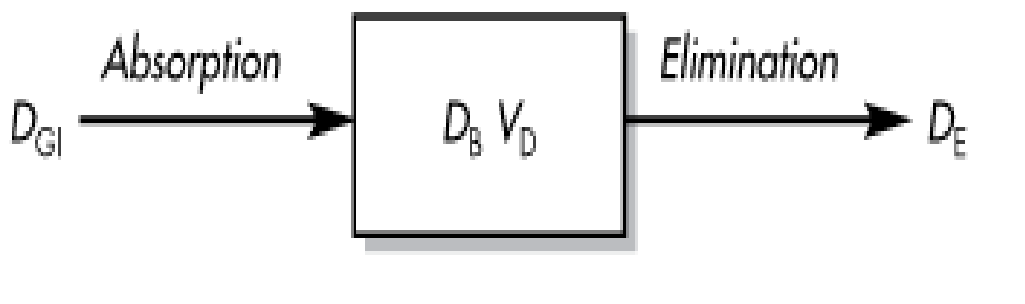
Pharmacokinetics of Drug Absorption

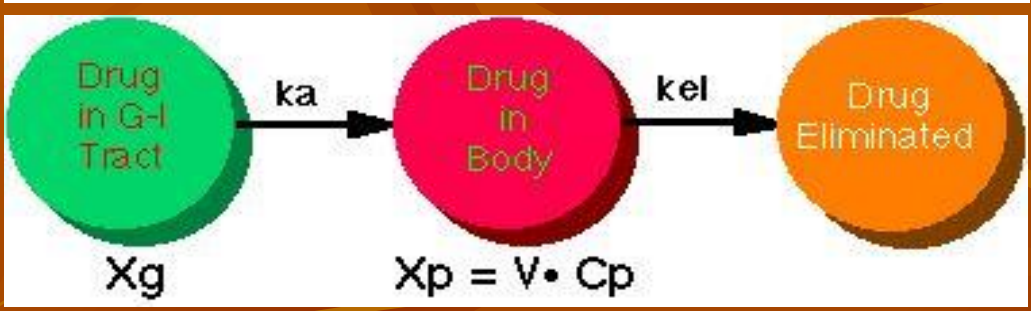
- Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.

- The rate of change in the amount of drug in the body, dD_B/dt, is dependent on the relative rates of drug absorption and elimination.

- The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption less the rate of drug elimination.

Pharmacokinetics of Drug Absorption





Where:

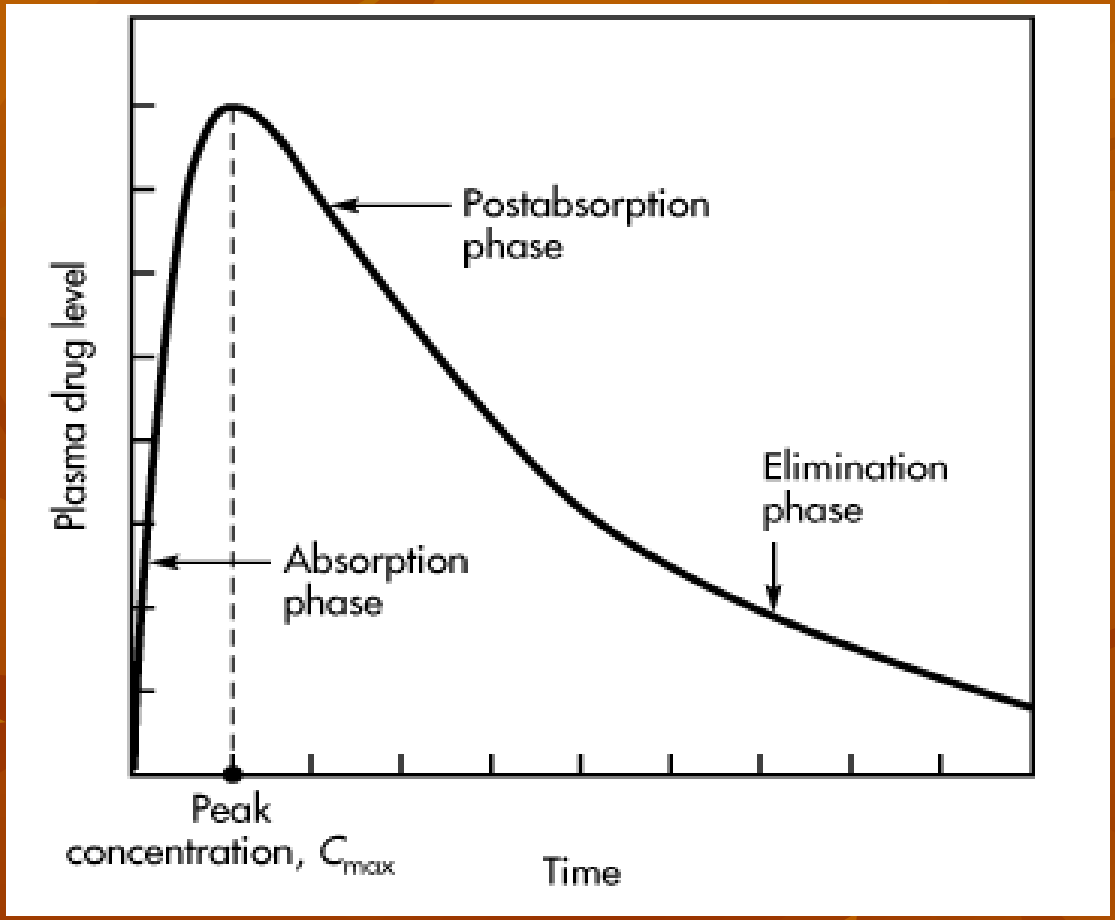
$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt}$$

D_{GI} is amount of drug in the gastrointestinal tract.

D_E is amount of drug eliminated.

- The drug absorption and elimination phases of the curve are shown:

Plasma level–time curve for a drug given in a single oral dose.



- During the *absorption phase* of a plasma level–time curve , the rate of drug absorption is greater than the rate of drug elimination.

Pharmacokinetics of Drug Absorption

- Note that during the absorption phase, elimination occurs *whenever* drug is present in the plasma, even though absorption predominates.

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt}$$

- At the peak drug concentration in the plasma, the rate of drug absorption just equals the rate of drug elimination, and there is no net change in the amount of drug in the body.

$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt}$$

Pharmacokinetics of Drug Absorption

- Immediately after the time of peak drug absorption, some drug may still be at the absorption site (ie, in the GI tract or other site of administration).

- The rate of drug elimination at this time is faster than the rate of absorption (the *postabsorption phase)*.

$$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}$$

- When the drug at the absorption site becomes depleted, the rate of drug absorption approaches zero, or

  $dD_{GI}/dt = 0$.

Pharmacokinetics of Drug Absorption

- The plasma level–time curve (now the *elimination phase*) then represents only the elimination of drug from the body, usually a first-order process.

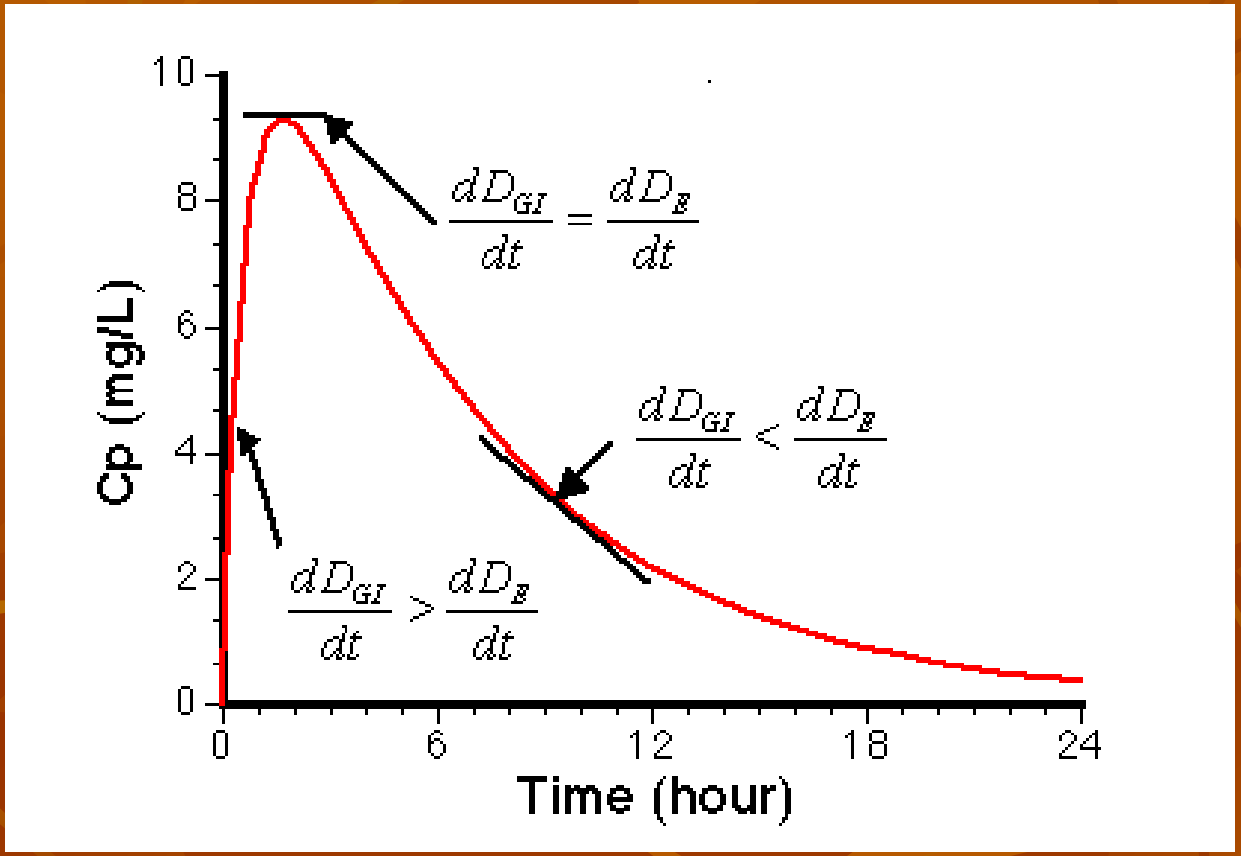
- During the elimination phase the rate of change in the amount of drug in the body is described as a first-order process,

$$\frac{dD_B}{dt} = -kD_B$$

where:

k is the first-order elimination rate constant.

Pharmacokinetics of Drug Absorption

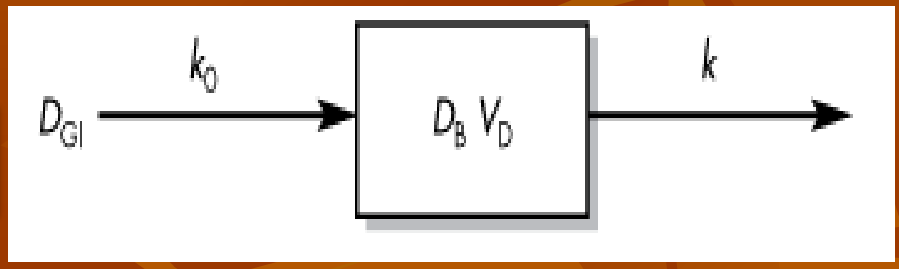


Linear Plot of Cp versus Time after Oral Administration

Zero-Order Absorption Model

- Zero-order drug absorption from the dosing site into the plasma usually occurs when either the drug is absorbed by **a saturable process** or a **zero-order controlled-release delivery system** is used.

- The pharmacokinetic model assuming zero-order absorption is described here.



One-compartment pharmacokinetic model for zero-order drug absorption and first-order drug elimination

- In this model, drug in the gastrointestinal tract, D_{GI}, is absorbed systemically at a constant rate, k_0.

- Drug is simultaneously and immediately eliminated from the body by a first-order rate process defined by a first-order rate constant, *k*. This model is analogous to that of the administration of a drug by intravenous infusion.

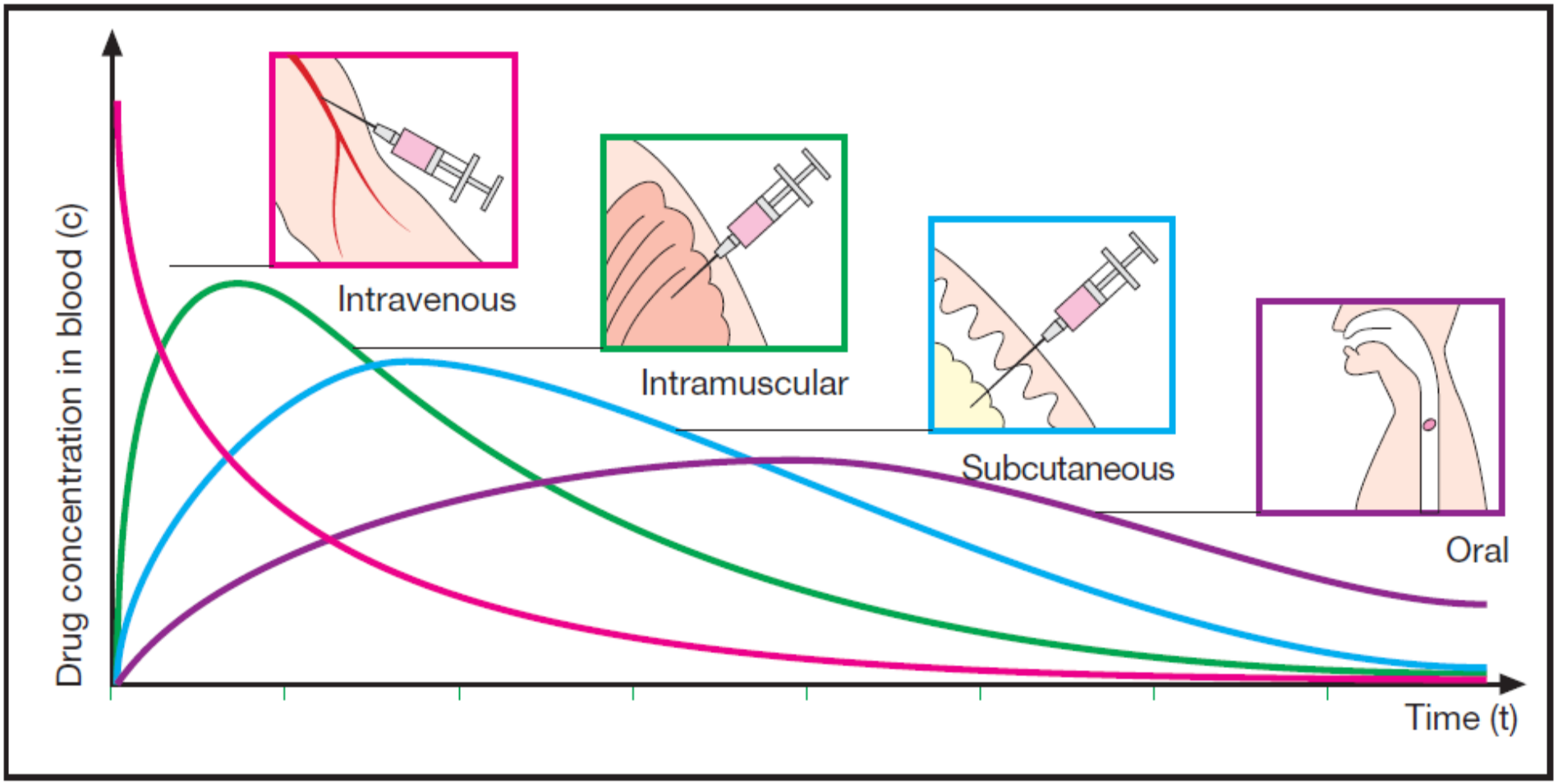
- The rate of first-order elimination at any time is equal to $D_B\,k$. The rate of input is simply k_0. Therefore, the net change per unit time in the body can be expressed as:

$$\frac{dD_B}{dt} = k_0 - kD_B \quad \text{integration of this Eq. with substition of } V_D C_P \text{ for } D_B$$

$$C_P = \frac{k_0}{V_D k}\left(1 - e^{-kt}\right)$$

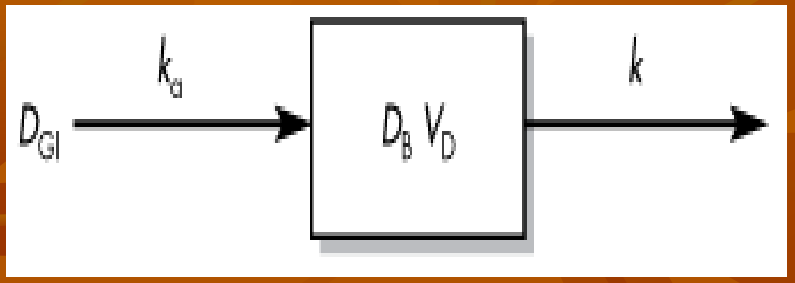
First-Order Absorption Model

- Absorption is usually assumed to be a first-order process.
- This model assumes a first-order input across the gut wall and first-order elimination from the body.
- This model applies mostly to the oral absorption of drugs in solution or rapidly dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories and drugs given by IM or SC aqueous injections.



B. Mode of application and time course of drug concentration

First-Order Absorption Model



One-compartment pharmacokinetic model for first-order drug absorption and first-order elimination.

- The rate of disappearance of drug from the gastrointestinal tract is described by:

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F$$

where :

k_a is the first-order absorption rate constant from the GI tract.
F is the fraction absorbed.
D_{GI} is the amount of drug in solution in the GI tract at any time t.

First-Order Absorption Model

- Integration of the previous equation gives:

$$\frac{dD_{GI}}{dt} = D_0 e^{-k_a t}$$

- The rate of drug change in the body, dD_B/dt, is:

$$\frac{dD_B}{dt} = rate\ in - rate\ out$$

$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_B$$

$$\frac{dD_B}{dt} = Fk_a D_0 e^{-k_a t} - kD_B$$

First-Order Absorption Model

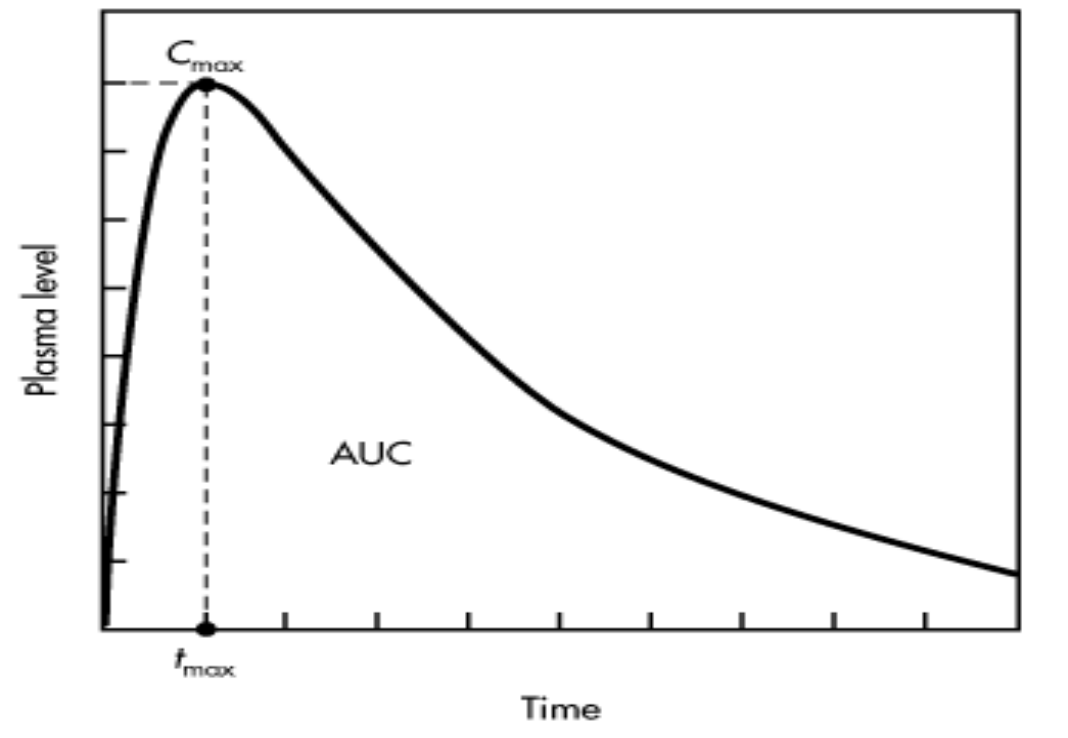
- The value of *F* may vary from 1 for a fully absorbed drug to 0 for a drug that is completely unabsorbed.

- This equation can be integrated to give the general oral absorption equation for calculation of the drug concentration (C_p) in the plasma at any time *t*,

$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)}\left(e^{-kt} - e^{-k_at}\right)$$

First-Order Absorption Model

- A typical plot of the concentration of drug in the body after a single oral dose is presented.



Typical plasma level–time curve for a drug given in a single oral close.

First-Order Absorption Model

- The maximum plasma concentration after oral dosing is C_{max}, and the time needed to reach maximum concentration is t_{max}.
- The t_{max} is independent of dose and is dependent on the rate constants for absorption (k_a) and elimination (k).
- At C_{max}, sometimes called *peak concentration*, the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero.

First-Order Absorption Model

- At C_{max}, the rate of concentration change can be obtained by:

$$t_{max} = \frac{\ln k_a - \ln k}{k_a - k} = \frac{\ln(k_a / k)}{k_a - k}$$

$$t_{max} = \frac{2.3 \log(k_a / k)}{k_a - k}$$

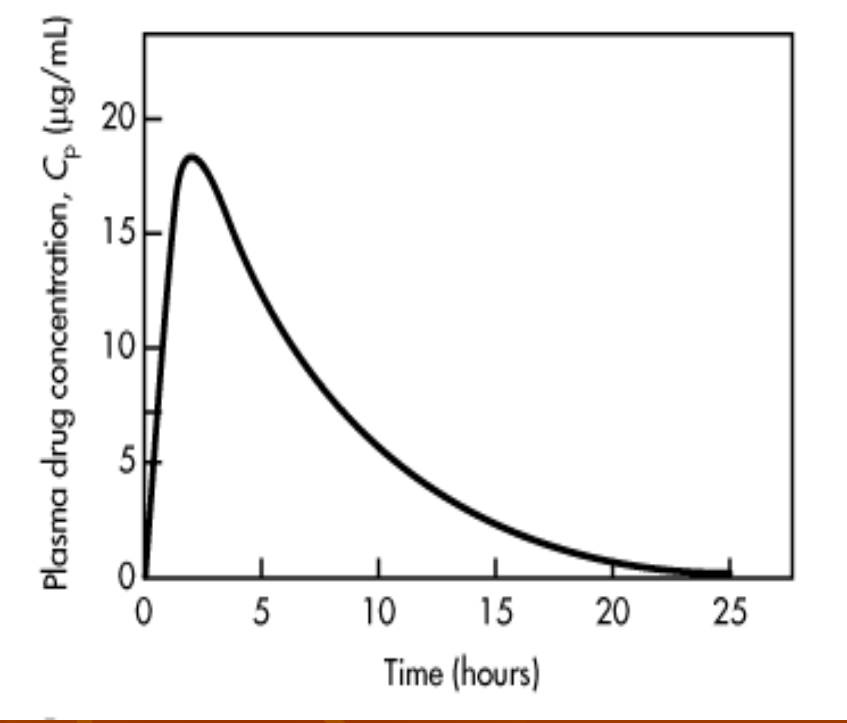
First-Order Absorption Model

- The first-order elimination rate constant may be determined from the elimination phase of the plasma level–time curve.
- At later time intervals, when drug absorption has been completed, ie, $e^{-kat} \approx 0$, Equation reduces to:

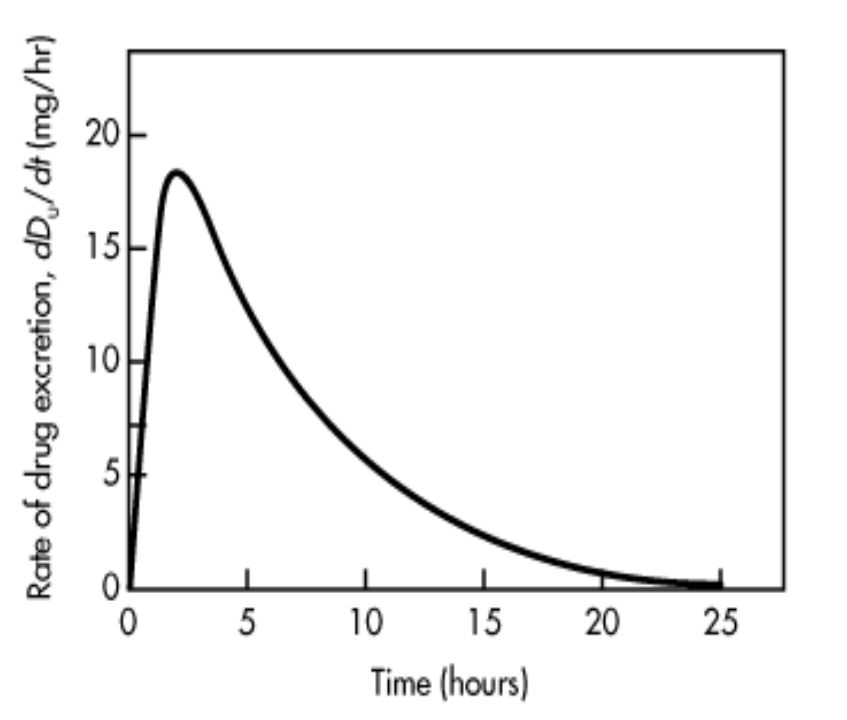
$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)} e^{-kt}$$

$$\log C_P = \log \frac{Fk_aD_0}{V_D(k_a - k)} - \frac{kt}{2.3}$$

First-Order Absorption Model



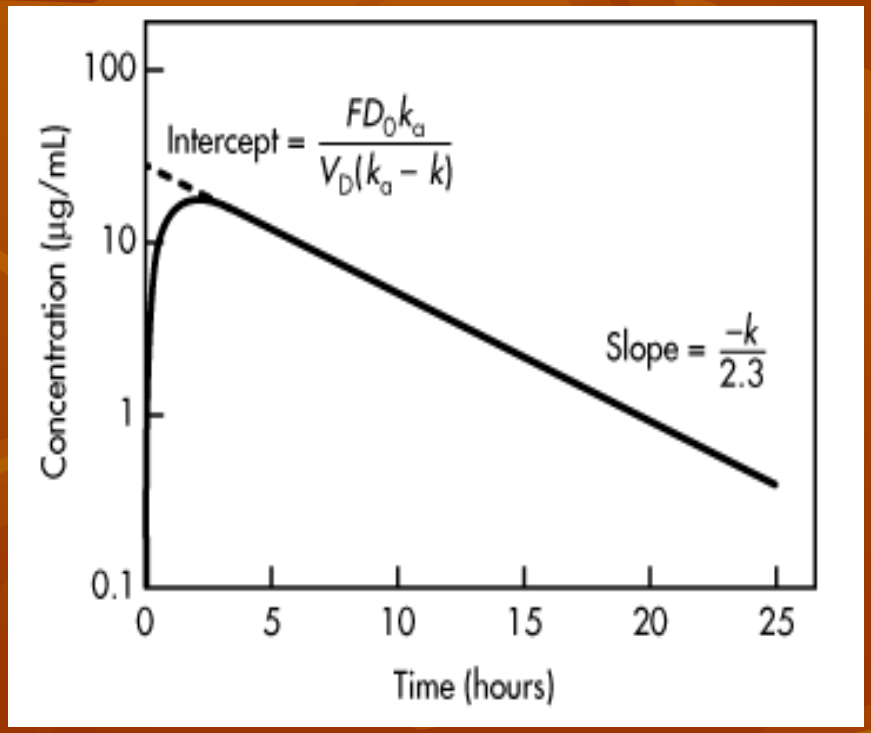
Plasma drug concentration versus time single oral dose.



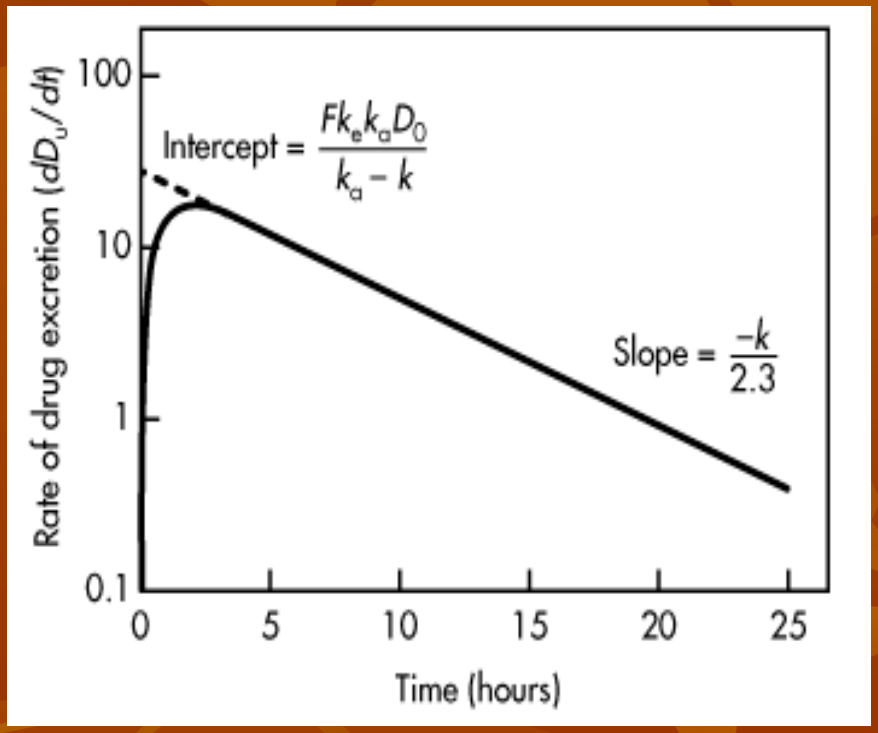
Rate of urinary drug excretion versus time single oral dose.

First-Order Absorption Model

- plotting log C_p versus time will yield a straight line with a slope of $-k/2.3$



Plasma drug concentration versus time single oral dose.



Rate of urinary drug excretion versus time single oral dose.

First-Order Absorption Model

- urinary drug excretion data may also be used for calculation of the first-order elimination rate constant.

- The rate of drug excretion after a single oral dose of drug is given by:

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k}\left(e^{-kt} - e^{-k_a t}\right)$$

- After drug absorption is virtually complete, $-e^{-k_a t}$ approaches zero, and Equation reduces to

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k} e^{-kt}$$

First-Order Absorption Model

- Taking the natural logarithm of previous eq.

$$\log \frac{dD_u}{dt} = \log \frac{Fk_a k_e D_0}{k_a - k} - \frac{kt}{2.3}$$

- When log (dD_u/dt) is plotted against time, a graph of a straight line is obtained with a slope of $-k/2.3$.

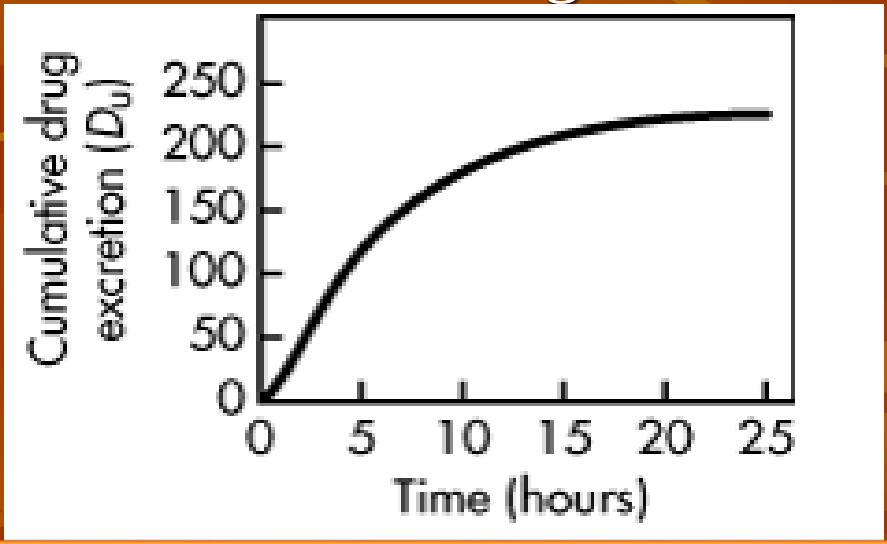
- Because the rate of urinary drug excretion, dD_u/dt, cannot be determined directly for any given time point, an average rate of urinary drug excretion is obtained, and this value is plotted against the midpoint of the collection period for each urine sample.

First-Order Absorption Model

- To obtain the cumulative drug excretion in the urine

$$D_u = \frac{Fk_a k_e D_0}{k_a - k}\left(\frac{e^{-k_a t}}{k_a} - \frac{e^{-kt}}{k}\right) + \frac{Fk_e D_0}{k}$$

- A plot of D_u versus time will give the urinary drug excretion curve:



Cumulative urinary drug excretion versus time single oral dose.

First-Order Absorption Model

- When all of the drug has been excreted, at $t = \infty$. Equ. reduces to:

$$D_u^{\infty} = \frac{Fk_e D_0}{k}$$

where: D^{∞}_u is the maximum amount of active or parent drug excreted.

Determination of Absorption Rate Constants from Oral Absorption Data

Method of Residuals

- When this is the case, drug absorption is virtually complete:

$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)}e^{-kt}$$

- The intercept of the *y* axis:

$$A = \frac{Fk_aD_0}{V_D(k_a - k)}$$

- Where *A* is a constant. Thus, Equ. Becomes:

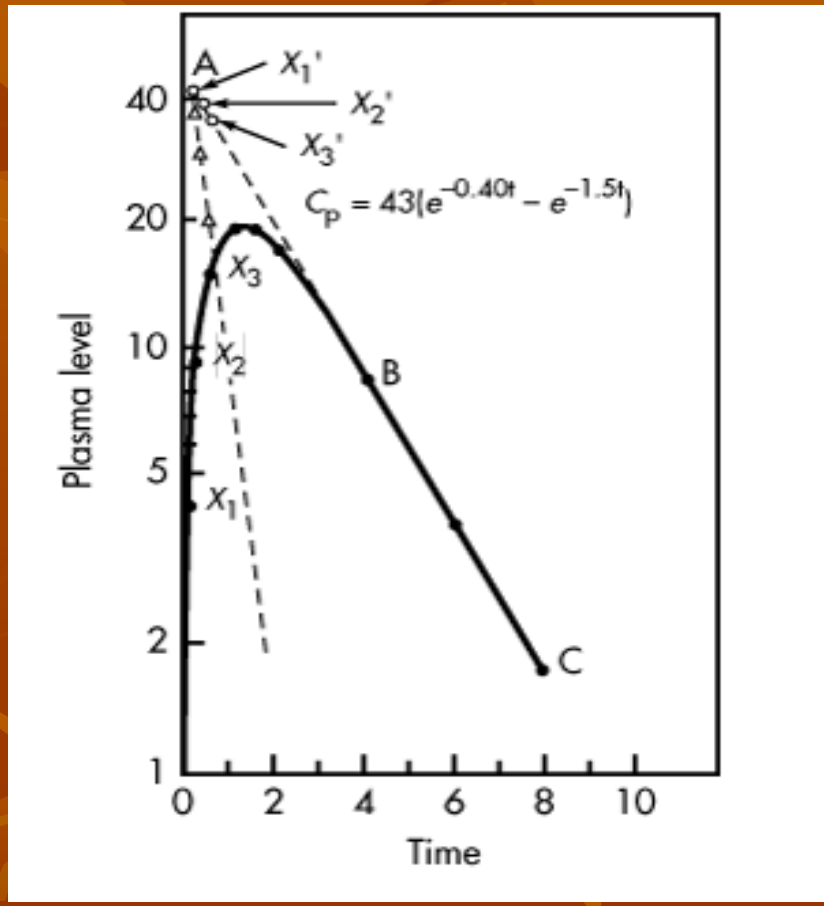
$$C_P = Ae^{-kt}$$

This equation represents first-order drug elimination.

Method of Residuals

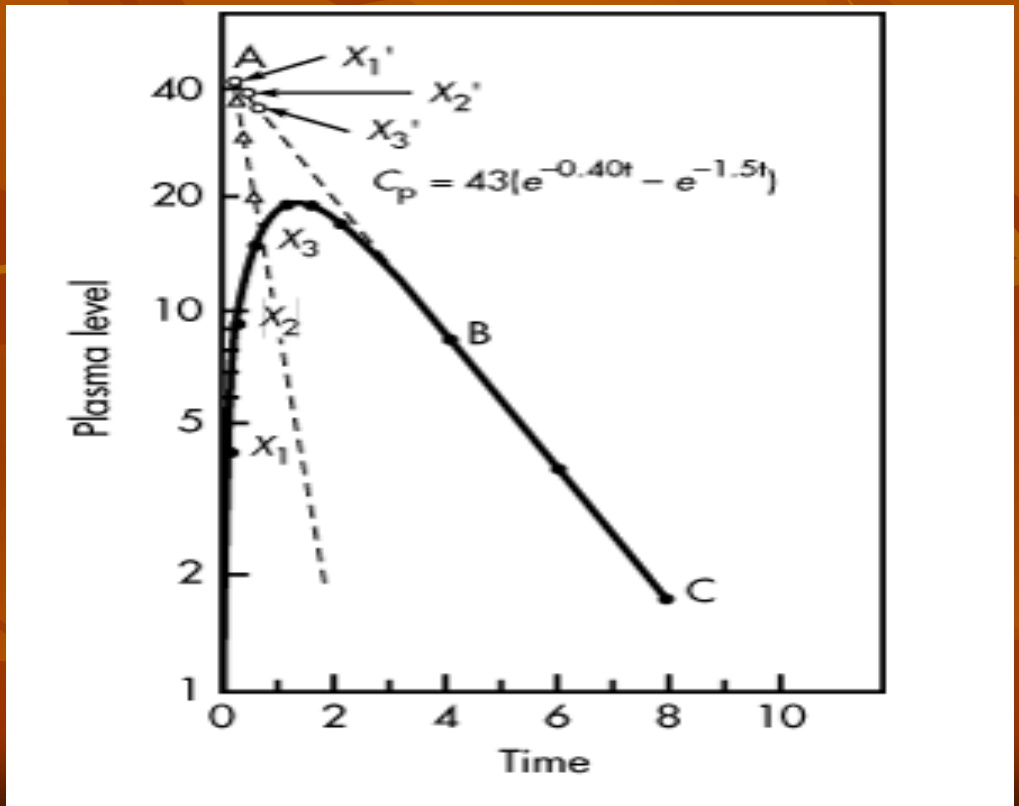
- The value of k_a is obtained by the following procedure:

1. Plot the drug concentration versus time on semilog paper.
2. Obtain the slope of the terminal phase (line *BC*,) by extrapolation.
3. Take any points on the upper part of line *BC* (eg, x'_1, x'_2, x'_3, . . .) and drop vertically to obtain corresponding points on the curve (eg, x_1, x_2, x_3,.)



Method of Residuals

4. Read the concentration values at x_1 and x'_1, x_2 and x'_2, x_3 and x'_3, and so on. Plot the values of the differences at the corresponding time points Δ_1, Δ_2, Δ_3, ... A straight line will be obtained with a slope of $-k_a/2.3$.



Method of Residuals

- When using the method of residuals, a minimum of three points should be used to define the straight line.

- Data points occurring shortly after t_{max} may not be accurate, because drug absorption is still continuing at that time. Because this portion of the curve represents the postabsorption phase, only data points from the elimination phase should be used to define the rate of drug absorption as a first-order process.

Method of Residuals

- If **drug absorption begins immediately** after oral administration, the residual lines obtained will intersect on the *y* axis at point *A*.

- The value of this *y* intercept, *A*, represents a hybrid constant composed of k_a, k, V_D, and FD_0. The value of *A* has no direct physiologic meaning.

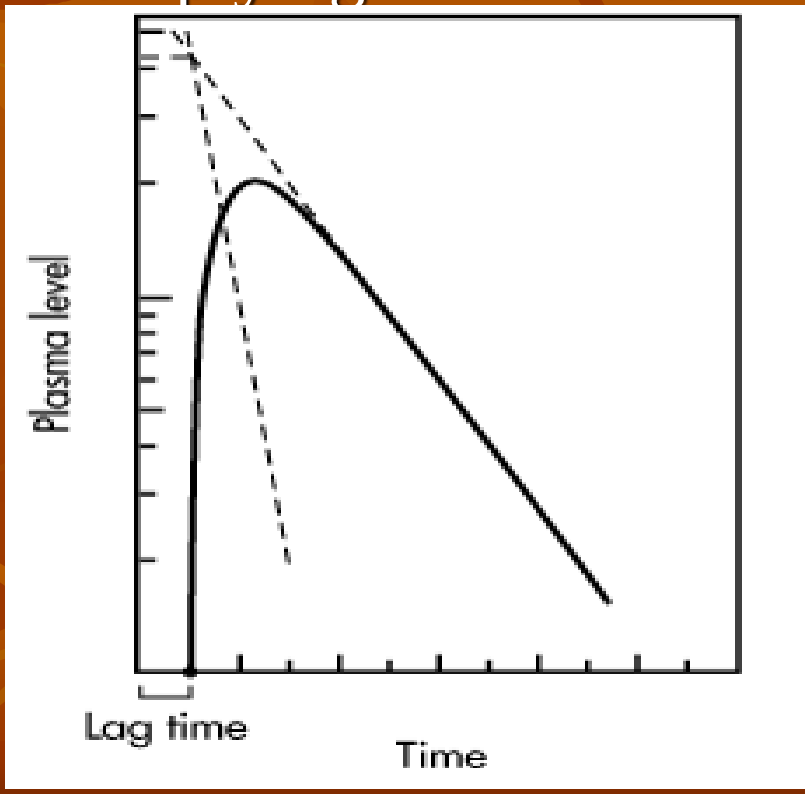
$$C_P = Ae^{-kt}$$

$$A = \frac{Fk_aD_0}{V_D(k_a - k)}$$

Lag Time

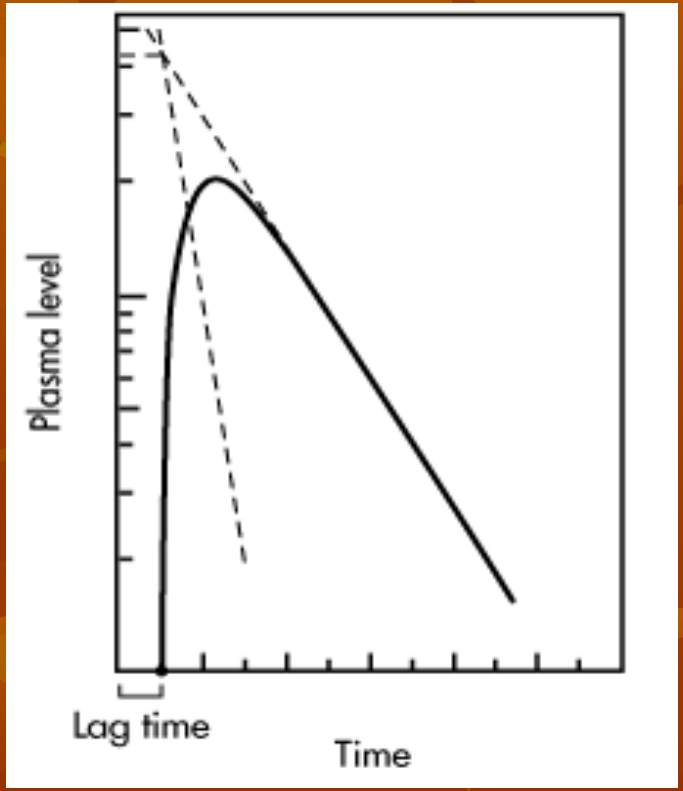
- In some individuals, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility.

The time delay prior to the commencement of first-order drug absorption is known as ***lag time***.



Lag Time

- The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level–time curve intersect at a point greater than $t = 0$ on the x axis.
- The time at the point of intersection on the x axis is the lag time.



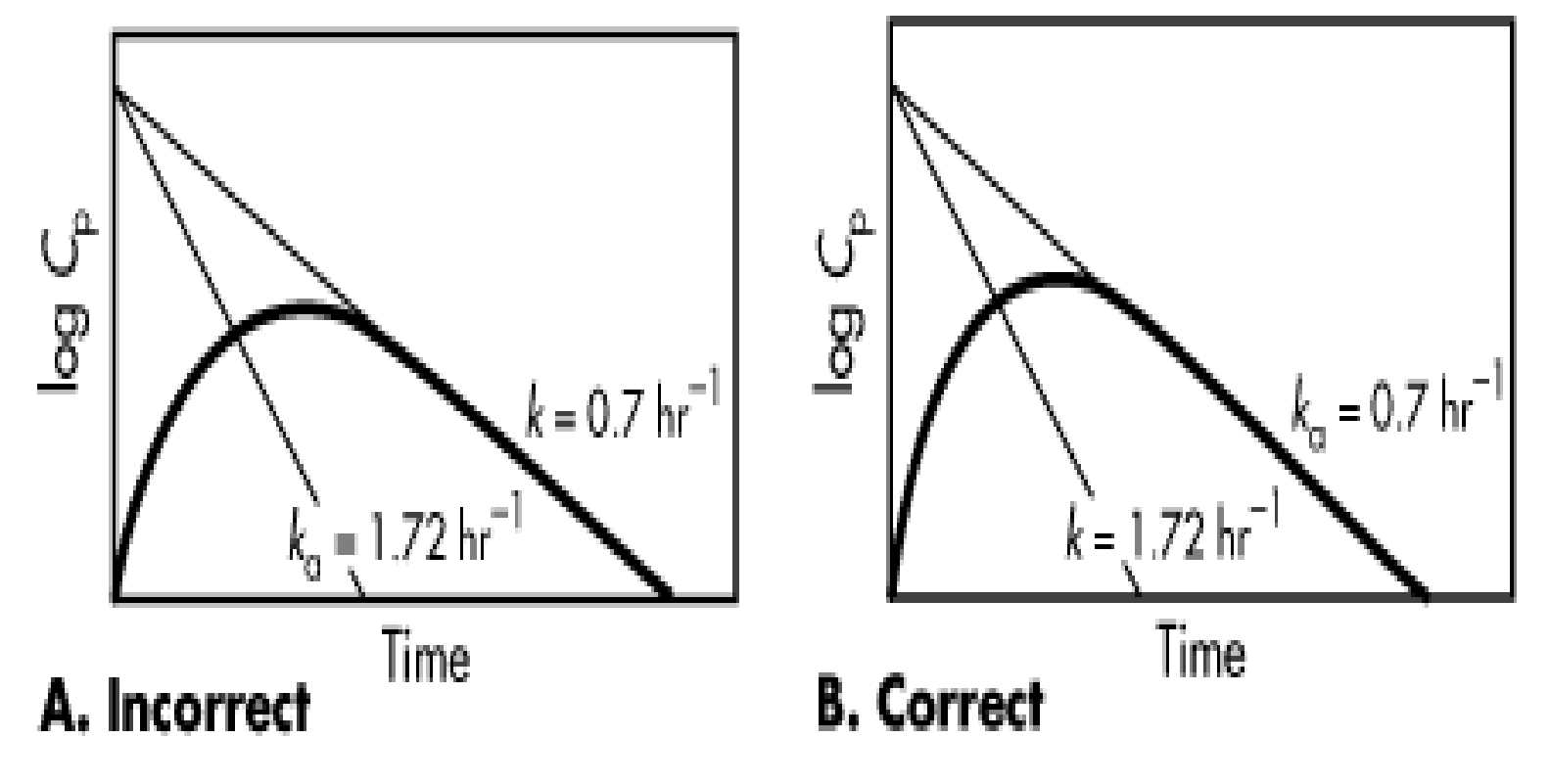
The lag time, t_0, represents the beginning of drug absorption and should not be confused with the pharmacologic term *onset time*, which represents latency, eg, the time required for the drug to reach minimum effective concentration.

Flip-Flop of k_a and k

- In a few cases, the elimination rate constant *k* obtained from oral absorption data does not agree with that obtained after intravenous bolus injection.

- For example, the *k* obtained after an intravenous bolus injection of a bronchodilator was 1.72 hr^{-1}, whereas the *k* calculated after oral administration was 0.7 hr^{-1}. When k_a was obtained by the method of residuals, the rather surprising result was that the k_a was 1.72 hr^{-1}.

Flip-Flop of k_a and k

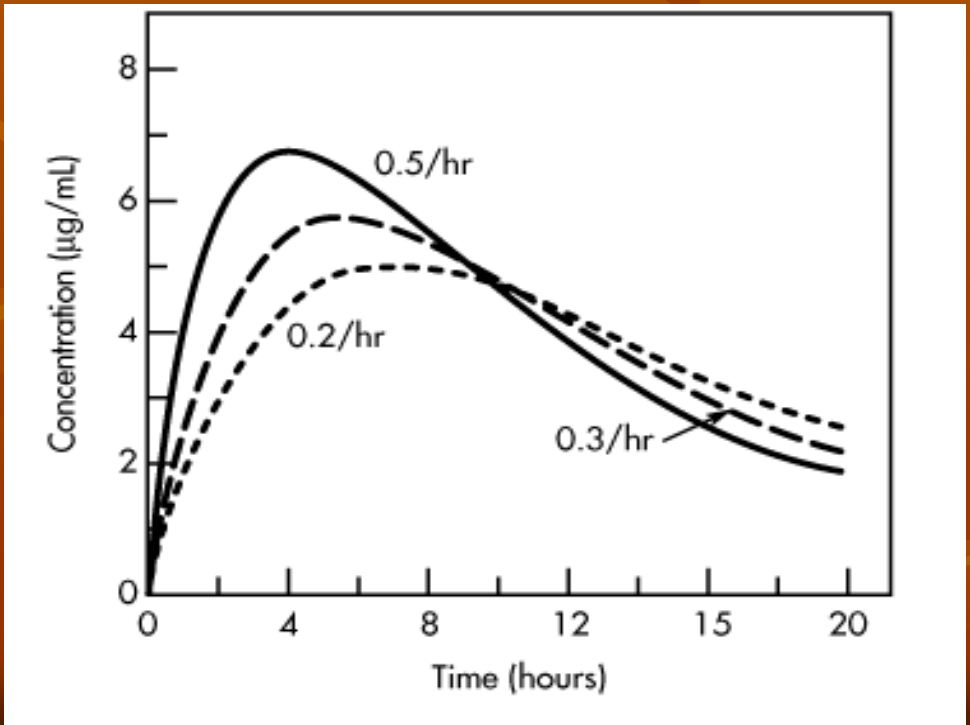


Flip-flop of k_a and k. Because $k > k_a$

Flip-Flop of k_a and k

- Most of the drugs observed to have flip-flop characteristics are drugs with fast elimination (ie, $k > k_a$).
- For drugs that have a large elimination rate constant ($k > 0.69$ hr^{-1}), the chance for flip-flop of k_a and k is much greater.
- Drugs with a large k are usually considered to be unsuitable for an oral drug product due to their large elimination rate constant, corresponding to a very short elimination half-life.
- An extended-release drug product may slow the absorption of a drug, such that the k_a is smaller than the k and producing a flip-flop situation.

- If the values for k_a and k are reversed, then the same t_{max} is obtained, but the C_{max} and AUC are different.
- If the elimination rate constant is kept at 0.1 hr^{-1} and the k_a changes from 0.2 to 0.6 hr^{-1} (absorption rate increases), then the t_{max} becomes shorter (from 6.93 to 3.58 hr), the C_{max} increases (from 5.00 to 6.99 μg/mL), but the AUC remains constant (100 μg hr/mL).



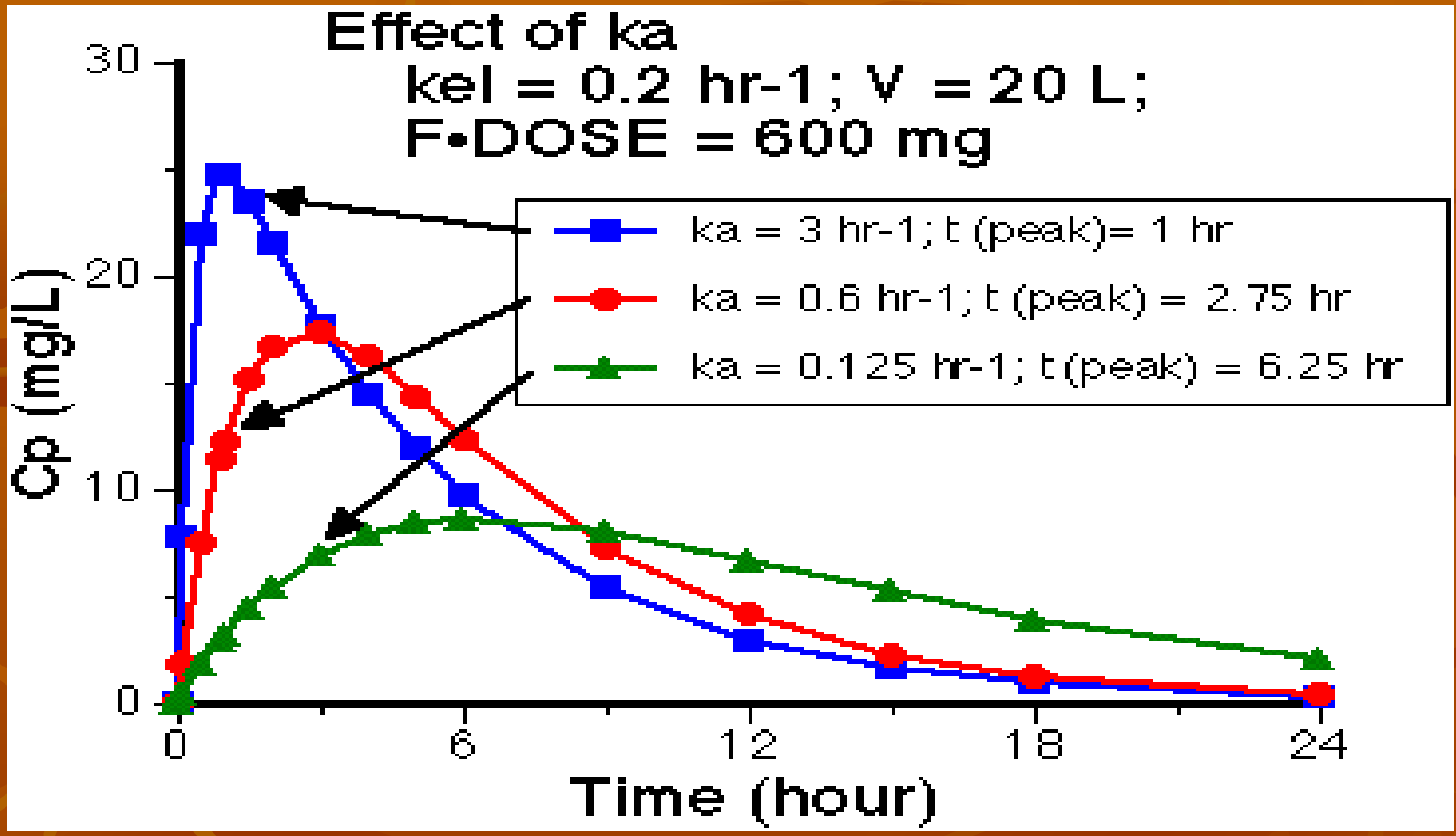
Effect of a change in the **absorption rate constant**, k_a, on the plasma drug concentration-versus-time curve.

Dose of drug is 100 mg, V_D is 10 L, and k is 0.1 hr^{-1}.

Effect of k_a and k on C_{max}, t_{max}, and AUC

Changes in k_a and k may affect t_{max}, C_{max}, and AUC as shown:

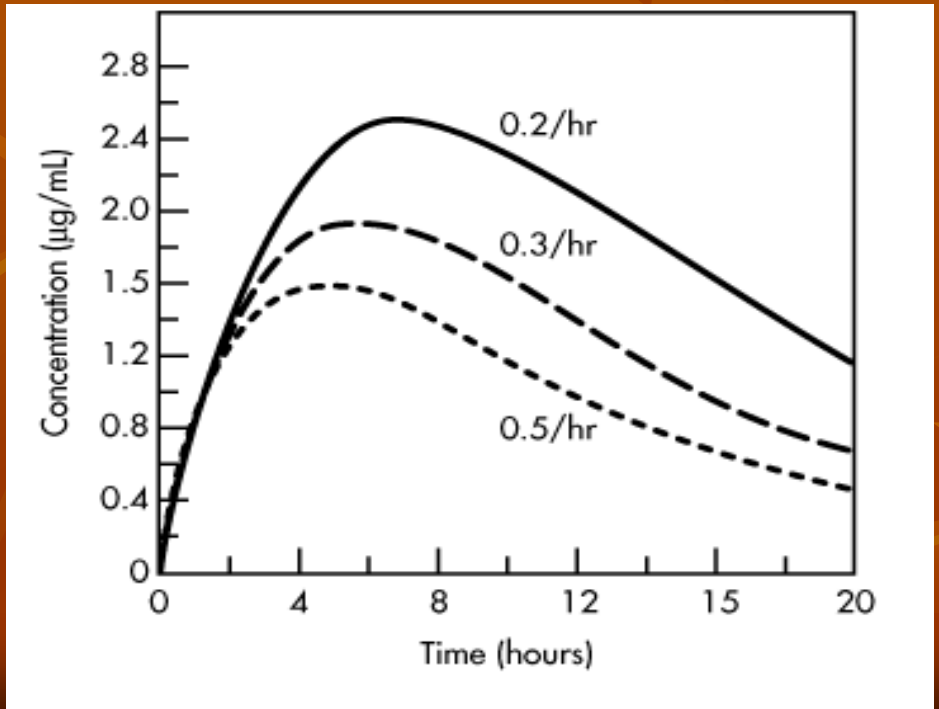
Absorption Rate Constant k_a (hr^{-1})	Elimination Rate Constant k (hr^{-1})	t_{max} (hr)	C_{max} (µg/mL)	AUC (µg hr/mL)
0.1	0.2	6.93	2.50	50
0.2	0.1	6.93	5.00	100
0.3	0.1	5.49	5.77	100
0.4	0.1	4.62	6.29	100
0.5	0.1	4.02	6.69	100
0.6	0.1	3.58	6.99	100
0.3	0.1	5.49	5.77	100
0.3	0.2	4.05	4.44	50
0.3	0.3	3.33	3.68	33.3
0.3	0.4	2.88	3.16	25
0.3	0.5	2.55	2.79	20



Notice that with higher values of ka the peak plasma concentrations are higher and earlier.

Effect of k_a and k on C_{max}, t_{max}, and AUC

- In contrast, when the absorption rate constant is kept at 0.3 hr^{-1} and *k* changes from 0.1 to 0.5 hr^{-1} (elimination rate increases), then the t_{max} decreases (from 5.49 to 2.55 hr), the C_{max} decreases (from 5.77 to 2.79 μg/mL), and the AUC decreases (from 100 to 20 μg hr/mL).



Effect of a change in the **elimination rate constant**, *k*, on the plasma drug concentration-versus-time curve.

Dose of drug is 100 mg, V_D is 10 L, and k_a is 0.1 hr^{-1}.

7. A single oral dose (100 mg) of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fits a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is

$$C_p = 45(e^{-0.17t} - e^{-1.5t})$$

From the equation above, calculate **(a)** t_{max}, **(b)** C_{max}, and **(c)** $t_{1/2}$ for the drug in this patient. Assume C_p is in μg/mL and the first-order rate constants are in h^{-1}.

8. Two drugs, A and B, have the following pharmacokinetic parameters after a single oral dose of 500 mg:

Drug	k_a (h^{-1})	k (h^{-1})	V_D (mL)
A	1.0	0.2	10,000
B	0.2	1.0	20,000

Both drugs follow a one-compartment pharmacokinetic model and are 100% bioavailable.

a. Calculate the t_{max} for each drug.

b. Calculate the C_{max} for each drug.

Homework (submit next lecture)

- Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows:

Time (hours)	Concentration (ng/mL)
0.25	2.85
0.50	5.43
0.75	7.75
1.00	9.84
2.00	16.20
4.00	22.15
6.00	23.01
10.00	19.09
14.00	13.90
20.00	7.97

- a. Determine the elimination constant of the drug.
- b. Determine k a by feathering.
- c. Determine the equation that describes the plasma drug concentration of the new benzodiazepine.
- d. the elimination half-life, t 1/2;
- e. the t max, or time of peak drug concentration.
- f. the volume of distribution of the drug.