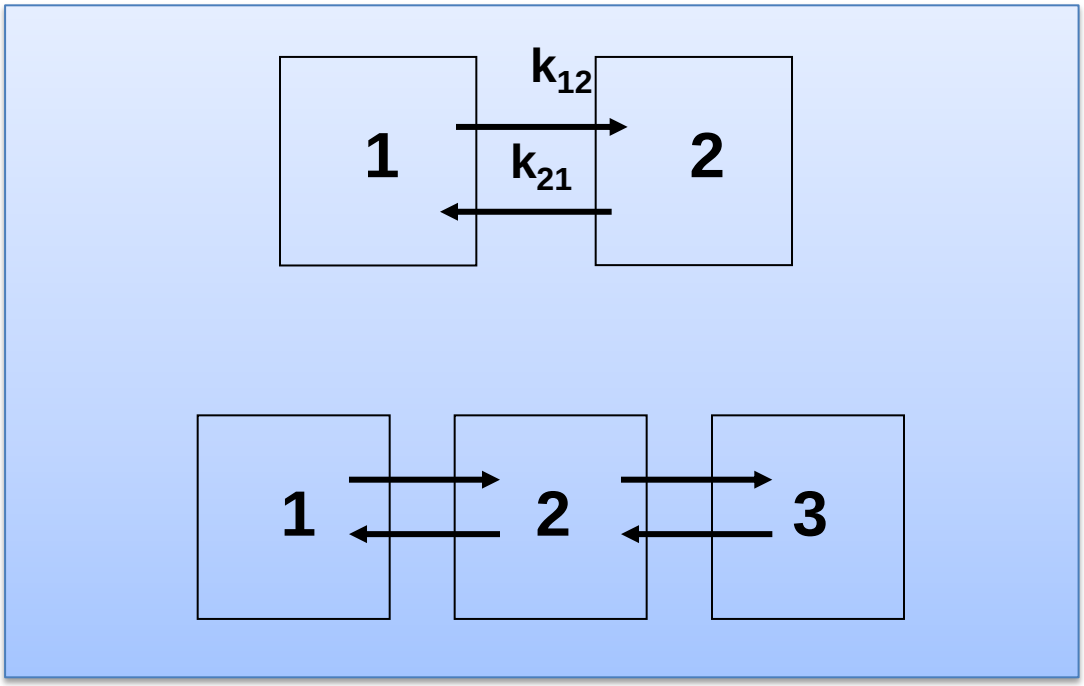
Clinical Ph.K Equations& Calculations

By

Lect. Shaimaa Saleh

COMPARTMENTAL MODELS

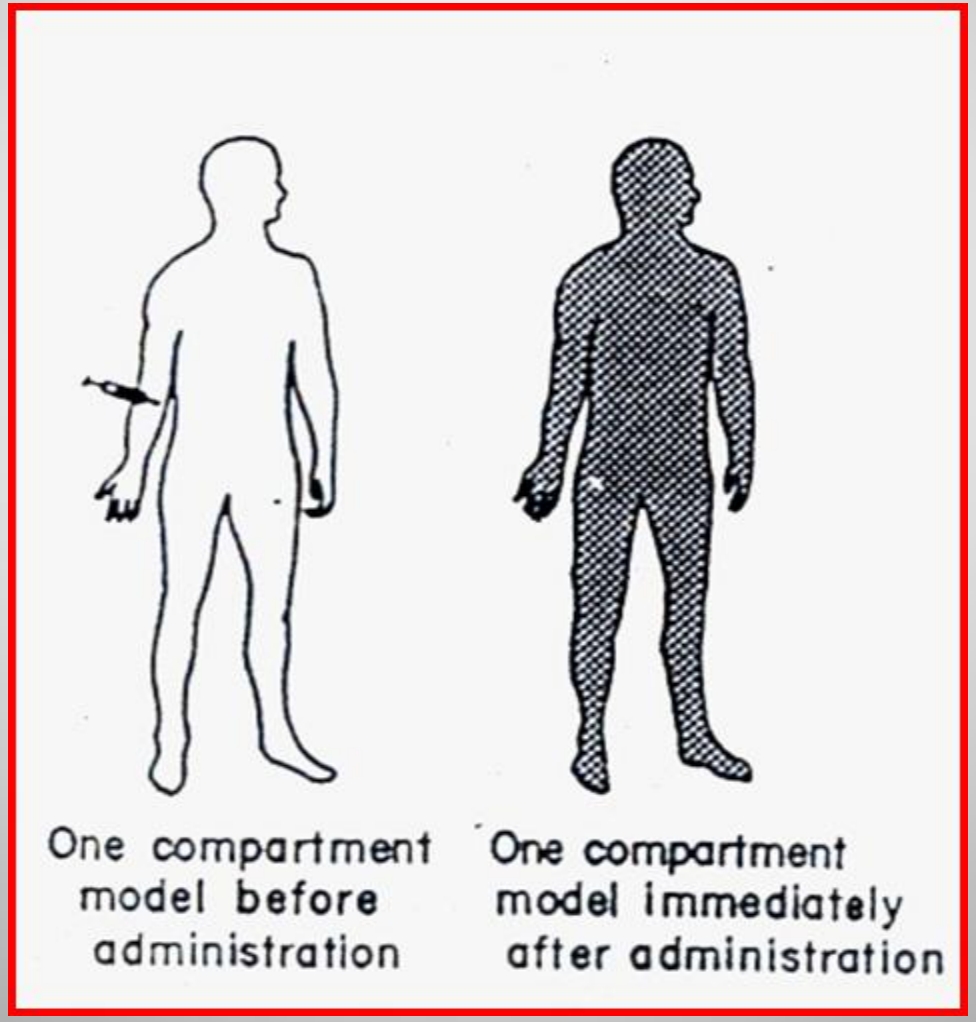
The body is represented by a series of compartments that communicate reversibly with each other.



- A compartment is not a real physiologic or anatomic region, but it is a tissue or group of tissues having similar blood flow and drug affinity.
- Within each compartment the drug is considered to be uniformly distributed.
- Drug move in and out of compartments
- Compartmental models are based on linear differential equations.
- Rate constants are used to describe drug entry into and out from the compartment.

- The model is an open system since drug is eliminated from the system.
- The amount of drug in the body is the sum of drug present in the compartments.
- Parameters are kinetically determined from the data.

One Compartment Open Model Intravenous Administration



ONE-COMPARTMENT MODEL EQUATIONS FOR LINEAR PHARMACOKINETICS

- When medications are administered to humans, the body acts as if it is a series of compartments. In many cases, the drug distributes from the blood into the tissues quickly, and a pseudoequilibrium of drug movement between blood and tissues is established rapidly. When this occurs, a one-compartment model can be used to describe the serum concentrations of a drug.

- In some clinical situations, it is possible to use a one-compartment model to compute doses for a drug even if drug distribution takes time to complete. In this case, drug serum concentrations are not obtained in a patient until after the distribution phase is over.

Intravenous Bolus Equation

- When a drug is given as an intravenous bolus and the drug distributes from the blood into the tissues quickly, the serum concentrations often decline in a straight line when plotted on semilogarithmic axes .

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.

- Most drugs given intravenously cannot be given as an actual intravenous bolus because of side effects related to rapid injection. 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 drug is not eliminated during the infusion time, intravenous bolus equations can still be used.

- 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 20 mg/L and 10 mg/L, respectively. By plotting the serum concentration/time data on semilogarithmic axes, the time it takes for serum concentrations to decrease by one-half can be determined and is equal to 4 days. The elimination rate constant can be computed using the following relationship:

✓ **$ke = 0.693/t_{1/2}$**

$= 0.693/4\ d = 0.173\ d^{-1}$

✓ **C_0 =15mg/l (by extrapolation)**

✓ **V=D/ C0**

=600mg /15(mg/l)

=40L

Alternatively, these parameters could be obtained by calculation without plotting the concentrations. The elimination rate constant can be computed using the following equation:

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

where t_1 and C_1 are the first time/concentration pair and t_2 and C_2 are the second time/concentration pair.

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

The volume of distribution can be calculated by dividing the dose by the serum concentration at time = 0. The serum concentration at time = zero (C_0) can be computed using a variation of the intravenous bolus equation:

$$C = C_0\, e^{-ket}$$

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

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

Either phenobarbital concentration can be used to compute C_0. In this case, the time/concentration pair on day 1 will be used (time = 1 d, concentration = 20 mg/L):

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

volume of distribution (V) is then computed:

$$V = D/C_0$$

= 600 mg / (15 mg/L) = 40L.

Continuous and Intermittent Intravenous Infusion Equations

- a one compartment model intravenous infusion equation can be used to compute concentrations (C) while the infusion is running:-

$$C = (k0/Cl)(1 - e^{-ket}) = [k0/(keV)](1 - e^{-ket})$$

where k0 is the drug infusion rate (in amount per unit time, such as mg/h or (g/min), Cl is the drug clearance (since Cl = keV, this substitution was made in the second version of the equation), ke is the elimination rate constant, and t is the time that the infusion has been running.

- If the infusion is allowed to continue until steady state is achieved, the steady-state concentration (Css) can be calculated easily

$$Css = k0 / Cl$$
$$= k0/ (keV)$$

- If the infusion is stopped, postinfusion serum concentrations ($C_{postinfusion}$) can be computed by calculating the concentration when the infusion ended (C_{end}) using the appropriate equation in the preceding paragraph, and the following equation:-

$$C_{postinfusion} = C_{end}\, e^{-ket\ postinfusion}$$

where k_e is the elimination rate constant and $t_{postinfusion}$ is the postinfusion time ($t_{postinfusion} = 0$ at end of infusion and increases from that point).

- **Pharmacokinetic constants can also be calculated for use in the equations**.
- If a steadystate concentration is obtained after a continuous intravenous infusion has been running uninterrupted for 3–5 half-lives, the drug clearance (Cl) can be calculated by rearranging the steady-state infusion formula:

$$Cl = k_0/Css..$$

- If the infusion did not run until steady state was achieved, it is still possible to compute pharmacokinetic parameters from postinfusion concentrations.
- The volume of distribution (V) can be computed using the following equation

$$V=\frac{k0(1-e^{-ke\ t\sim})}{Ke[Cmax-(C_{predose}\, e^{-Ket\sim})]}$$

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 $k_e = 0.139\ h^{-1}$.The serum concentration of theophylline in this patient after receiving the drug for 8 hours and at steady state can be calculated:

$$C=[k0/(keV)](1 - e^{-ket})$$

$$Css = k0/ (keV)$$

- It is possible to compute the theophylline serum concentration 6 hours after the infusion stopped . If the infusion only ran for 8 hours, the serum concentration 6 hours after the infusion stopped would be

$$C_{postinfusion} = C_{end}\, e^{-ket\ postinfusion}$$

N.B:- C_{end} = **Css if the infusion ran until steady state was achieved.**

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 semilogarithmic axes after drug absorption is complete, a one compartment model extravascular equation can be used to describe the serum oncentration/time curve:

$$C = \{(FkaD) / [V(ka - ke)]\}(e^{-ket} - e^{-kat})$$

- When only postabsorption, postdistribution serum concentrations are obtained for a drug that is administered extravascularly, the equation simplifies to:

$$C = [(FD)/V]e^{-ket}$$

where C is the concentration at any postabsorption, postdistribution time; F is thebioavailability fraction; D is the dose; V is the volume of distrib; ke is the elimination rate constant; and t is any postabsorption, postdistribution time.

- Pharmacokinetic constants can also be calculated and used in these equations.
- If two or more postabsorption, postdistribution serum concentrations are obtained after an extravascular dose, the volume of distribution, elimination rate constant, and half-life can be computed

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

$$T1/2=\frac{0.693}{Ke}$$

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

$$V/F = D/C_0$$

- **An example:-** a patient that is administered 500 mg of oral procainamide as a capsule. It is known from prior clinic visits that the patient has a half life equal to 4 hours, an elimination rate constant of 0.173 h^{-1} and a volume of distribution of 175 L. The capsule that is administered to the patient has an absorption rate constant equal to 2 h^{-1} , and an oral bioavailability fraction of 0.85. The procainamide serum concentration 4 hours after a single dose would be equal to:

$$C = \{(FkaD) / [V(ka - ke)]\}(e^{-ket} - e^{-kat})$$

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 steady state is achieved.
- 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 factor

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

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.

- At steady state, the number of doses (n) is large,therefore, the steady-state version of the multiple dosing factor becomes the following:

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

where k_e is the elimination rate constant found in the exponential of the single dose equation and τ is the dosage interval.

Average Steady-State Concentration Equation

- A very useful and easy equation can be used to compute the average steady-state concentration (Css) of a drug:-

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

where F is the bioavailability fraction, D is the dose, τ is the dosage interval, and Cl is the drug clearance

- 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:

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

Where D is dose and τ is the dosage interval

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

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	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/C_0$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = D/(C_0 - C_{predose})$ $Cl = k_eV$
Continuous intravenous infusion	N/A	N/A	$Cl = k_0/Css$
Intermittent intravenous infusion	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose}e^{-k_e t'})]\}$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose}e^{-k_e t'})]\}$ $Cl = k_eV$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V = [k_0(1 - e^{-k_e t'})] / \{k_e[C_{max} - (C_{predose}e^{-k_e t'})]\}$ $Cl = k_eV$
Extravascular (postabsorption, postdistribution)	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/C_0$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$	$k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$ $t_{1/2} = 0.693/k_e$ $V/F = D/(C_0 - C_{predose})$ $Cl/F = k_e(V/F)$
Average steady-state concentration (any route of administration)	N/A	N/A	$Cl/F = (D/\tau)/Css$

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

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

MULTICOMPARTMENT MODELS

- When serum concentrations decrease in a rapid fashion initially and then decline at a slower rate later, a multicompartment model can be used to describe the serum concentration/time curve.

- The reason serum concentrations drop so rapidly after the dose is given is that all of the drug is in the bloodstream initially, and drug is leaving the vascular system by distribution to tissues and by hepatic metabolism and/or renal elimination. This portion of the curve is called the *distribution phase*. After this phase of the curve is finished, drug distribution is nearly complete and a psuedoequilibrium is established between the blood and tissues. During the final part of the curve, serum concentrations drop more slowly since only metabolism and/or elimination are taking place. This portion of the curve is called the *elimination phase*, and the elimination half-life of the drug is measured in this part of the serum concentration/time graph.

- Digoxin, vancomycin, and lidocaine are examples of drugs that follow multicompartment pharmacokinetics.

- In order to get accurate values for the pharmacokinetic constants in the equation, 3–5 serum concentrations for each phase of the curve need to be obtained after a dose is given to a patient. Because of the cost and time involved to collect 6–10 serum concentrations after a dose, multicompartment models are rarely used in patient care situations.

- If a drug follows multicompartment pharmacokinetics, serum concentrations are usually not drawn for clinical use until the distribution phase is over and the elimination phase has been established.

- In these cases, it is possible to use simpler one compartment model equations to compute doses with an acceptable degree of accuracy.