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Therapeutic Drug Monitoring(TDM)

Clinical Pharmacokinetic Equations and Calculations

Pharmacokinetic Models

Pharmacokinetic models are relatively simple mathematical schemes that represent complex physiologic spaces or processes. The most commonly used pharmacokinetic models are:

1:- One compartment model

2:- Multicompatment model

One compartment model

In the one-compartment model, the body is described as a single, uniform compartment into which the drug is administered and from which it is eliminated. This is a very 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 does not predict actual drug concentrations in the various tissues but assumes that drug tissue concentrations will be proportional to the drug plasma concentrations. If a drug rapidly equilibrates with the tissue compartment, which uses only one volume term, the apparent volume of distribution, Vd. A log scale plot of the serum level decay curve of a l-compartment model yields a straight line. e.g., aminoglycosides.

Multicompartment models (Two compartment model)

* The simplest multicompartment model is a two-compartment model which represents the body as a central compartment into which drug is administered and a peripheral compartment into which drug distributes. The central compartment is composed of blood and tissues which equilibrate rapidly with blood. The peripheral compartment represents tissues that equilibrate slowly with blood.

* Drugs which exhibit 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.

One-compartment model equations for linear pharmacokinetics:

Intravenous Bolus Equation

•Used when-:

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

B-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.

C-If 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- ompartment model intravenous bolus equation can be used:

$$\mathbf{C = (D/V)e^{-ket}}$$

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, Vis the volume of distribution, and ke is the elimination rate constant.

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

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

$ke = -(\ln C_1 - \ln C_2) / (t_1 - t_2)$

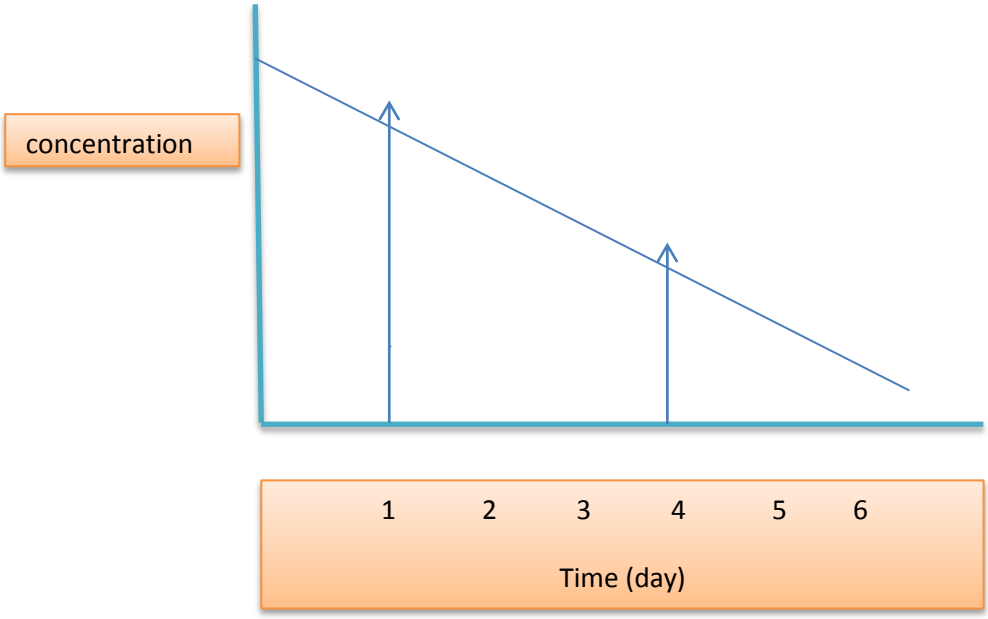
For example, a patient is given a theophylline loading dose of 400 mg intravenously over 20minutes. Because the patient received theophylline during previous hospitalizations, it is known that the volume of distribution is

30 L, the elimination rate constant equals $0.115h^{-1}$, and the half-life ($t_{1/2}$) is ($t_{1/2}$=0.693/ke =0.693/0.115 h=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:

$C= (D/V)\, e^{-ket} = (400\ mg/30L)\, e^{-(115h-1)(4\ h)} = 8.4\ mg/L.$

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 mgL and 7.5 mgL, respectively.



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

$$\mathbf{K_e = -(\ln C_1 - \ln C_2) / (t_1 - t_2)}$$

Where tl and Cl are the first time/concentration pair and t_2 and C_2 are the second time/concentration pair,

Ke =-[In (12.6 mg/L) - In (7.5 mg/L)]/ (1 d- 4d)= 0.173 d.

2- The elimination rate constant can be converted into the half-life using the following equation: tl/2=0.693/0.173 dl=4 d.

3- The serum concentration at time = zero (C_o) (the initial concentration) can be computed using a variation of the intravenous bolus equation:

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

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

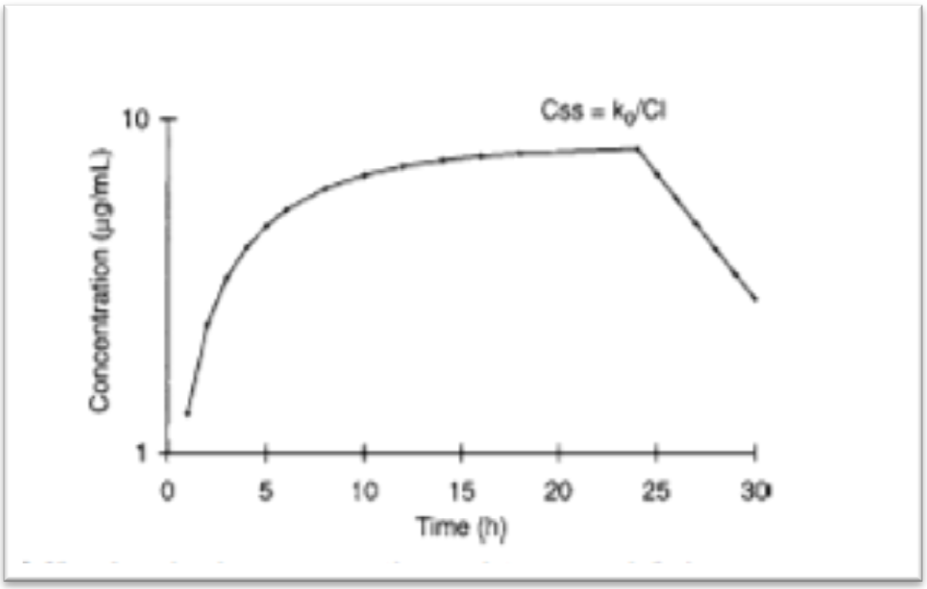
Either phenobarbital concentration can be used to compute C_o. In this case, the time/concentration pair on day l will be used (time l=d, concentration = 12.6 mg/L): $C_o = C / e^{-ket}$ = (12.6 mg/L) ⁄e-(0.173 d-1)(1 d) = 15.0 mg/L.

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 a semi logarithmic axes



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

A-while the infusion is running:

$C= (k_o/CI)(1 – e^{-ket}) = [k_o/(keV)](1 –eket)$

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

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

$Css = k_o/Cl = k_o/(kV)$

C-If the infusion is stopped

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

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

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 SteadyState can be calculated: $C= [k_o/(keV)](1 - e^{-ket}) = [(60mg/h) (0.139\ h\text{-}1\ 40\ L)] (1 - e^{-(0.139\ h\text{-}1)(8\ h)}) = 7.2\ mg/L$؛

$Css = k_o (k_eV) = (60\ mg/h)) (0.139\ h^{-1} . 40\ L) = 10.8\ mg/L.$

It is possible to compute the theophylline serum concentration 6 hours after the infusion stopped in either circumstance. If the infusion only ran for 8 hours, the serum concentration 6 hours after the infusion stopped would be: e

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

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

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

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

$10.8 mgL\ e^{-(0.139\ h\text{-}1)(6\ h)} = 4.7\ mg/L.$

The volume of distribution (V)

Can be computed using the following equations

1 - At steady state and when we know C_o

$V = Dose / C_o$ or $V = Cl / K$

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

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

•$C_{predose}$ = used only if we have multiple dose and we have predose concentration but when we are in first dose or Cpredose 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

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

where t is the tine 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 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.

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

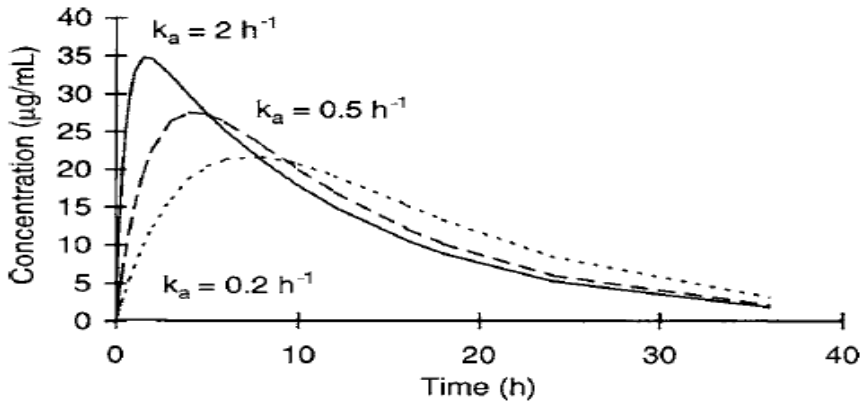


FIGURE :- Serum concentration/time curves for extravascular drug administration for agents following a one-compartment pharmacokinetics. The absorption rate constant (k_a) controls how quickly the drug enters the body. A large absorption rate constant allows drug to enter the body quickly while a small absorption rate constant permits drug to enter the body more slowly.

•After the end of a bsorption phase the C can be calculated by equation of I.V bolus

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

The hybrid volume of distribution/bioavailability (V/E) parameter

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

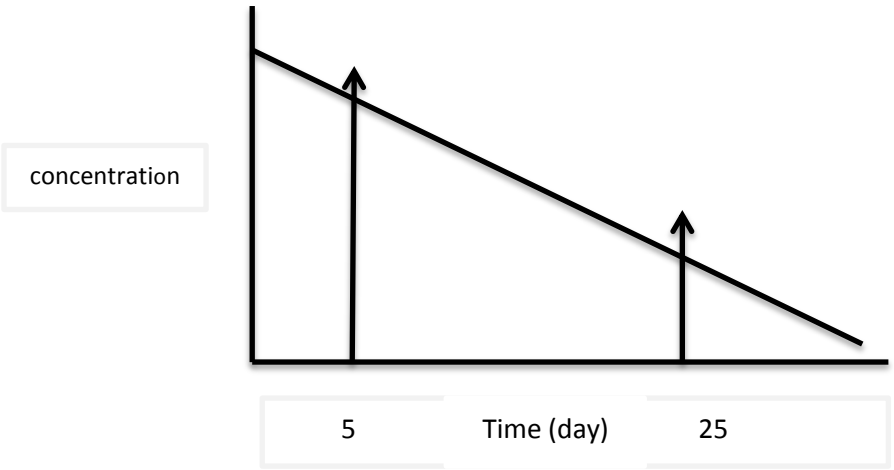
V/F= D/Co... .....or

V= D/ [C_o - $C_{predose}$], if not first dose

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

Ke =- (ln C_l - In C_2) /(t_1 - t_2)

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



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

ke =- (In C_1 - In C_2) / (t_1 - t_2)

where C1 is the first concentration at time = tl, and C2 is the second concentration at time = t_2

ke =- [ln (51.9 mg/L) - In (21.3 mg/L)/ (6 h - 24 h) = 0.0495 h^{-1}.

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

T1⁄2 =0.693/ke = 0.693/0.0495 h = 14 h.

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

Co = C/e^{-ket} = (21.3 mg/L) /e – (0.0495 h-1) (24 h) = 70 mg/L. The hybrid volume of distribution/bioavailability constant (V/F) is then computed: V/F = D/C_o =750 mg/ (70 mg/L) = 10.7 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 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 single dose equation to the multiple dose version, it is necessary to multiply each exponential term in the equation by the multiple dosing factor:

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

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

Example: the equation for multiple dose of intermittent IV will be:

$$C = (D/V)[e^{-k_e t}/\left(1 - e^{-k_e\tau}\right)$$

Multiple-Dose at steady state

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

Example: the equation for multiple dose of IV bolus at steady state will be :

$$\mathbf{C= (D/V)[e^{-ket} /(1 - e^{-ke\tau})]}$$

* **Average Steady-State Concentration Equation**

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

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

•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 phamacokinetic constant clearance/bioavailability (CVF) can be computed:

Cl/F = (D/t)/Css

Designing individualized dosage regimens using one compartment model equations

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

•Note: T 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, ke=0.05 h^{-1}, T_{max} = 3 h, F= 1.0) and maintain steady-

state maximum (Css_{max}) and minimum (Css_{min}) concentrations of 80 mg/L and 50 mgL, respectively:

τ=[(In Csmax-In Csmin)/(ke] + Tmax = [(In 80 mg/L - In 50 mg/L) /0.05 h]+3 h= 12.4 h, round to practical dosage interval of 12 h

D= [(Cssmax V)/ F] [(1 - ekeτ/ $e^{-keTmax}$] =

[(80 mg/L· 12 L)/1.0)][(1 - $e^{-0.05\ h\text{-}1(3hr)}$] =503 mg , round to practical dose of 500 mg. The patient would be prescribed valproic acid capsules 500 mg orally every 12 hours.