Two Compartment Body Model and V_d Terms

by

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In a one-compartment model, we make two important assumptions:

(1) Linear pharmacokinetics - By this, we mean that elimination is first order and that pharmacokinetic parameters (ke, Vd, Cl) are not affected by the amount of the dose. Of course, a change in dose will be reflected by a proportional change in plasma concentration.

(2) Immediate distribution and equilibrium of the drug throughout the body.

Considering these assumptions, we can easily describe the Cp vs t profile of a drug after an iv bolus injection (the same principles apply to other routes of administration as well) by the exponential equation:

$$Cp(t) = C_{p_0} \bullet e^{-k_e t}$$

$$= \frac{Dose}{V_d} \bullet e^{-k_e t}$$
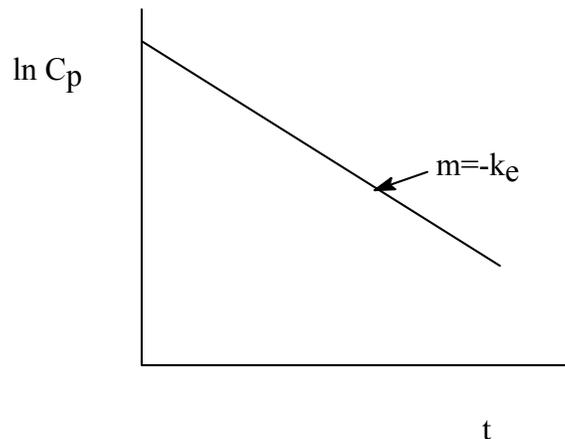
Since immediate distribution is assumed, the whole body is treated as one unit. The slope of the graph represents the total elimination constant of the drug out of the body regardless of the elimination pathway: $k_e = k_{ren} + k_{met} + k_{bil} + \ldots$

This one compartment model can often be used to predict Cp vs t profile and other pharmacokinetic parameters. The truth is, however, that very few drugs show immediate distribution and equilibrium through the body. If distribution is minimal, the one compartment can be an adequate approximation. (We want to use the simplest model we can). If not, we must alter the model to better fit the data. The "next step up" is the Two-Compartment body Model which includes a peripheral compartment into which the drug may distribute.
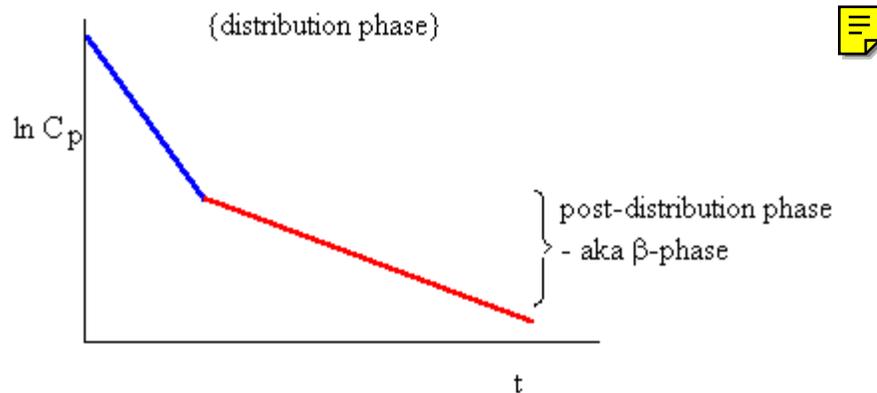
THE TWO COMPARTMENT MODEL
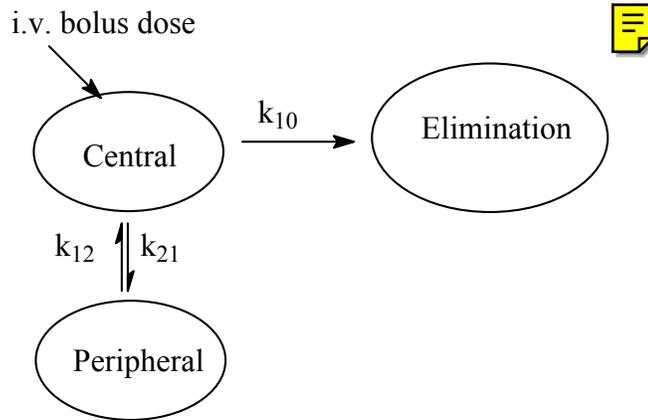
Although these compartments do not necessarily have a physiological significance, common designations are:

Comp 1 (central) - blood and well perfused organs, e.g. liver, kidney, etc.; "plasma"

Comp 2 (peripheral) - poorly perfused tissues, e.g. muscle, lean tissue, fat; "tissue"

A typical Cp vs t profile for this model is:

Obviously an equation with only one exponential term cannot describe this curve; Two are required.

$$C_{p(t)} = ae^{-\alpha t} + be^{-\beta t}$$

a, b, α, and β are called "hybrid constants". This form is much simpler than the analogous equation expressed in terms of the "hybrid constants" (k_{10}, k_{12}, k_{21}) and dose. α and β may be written in rather long expressions of the microconstants. A and b, in turn, can be expressed in terms of α, β, microconstants, and dose (and Vc - more later on the volume term.

The hybrid constants a, b, α, and β may be found by "feathering" which allows us to separate distribution and elimination (similar to the way we found k_a and k_e in oral administration).

Procedure:

1) Graph Cp vs t on ln (or log) scale

2) Extrapolate the terminal slope back to the y-axis. Call this extrapolated line Cp'; the y-intercept is b.

3) For several time points determine (Cp-Cp') and plot these points. Connect them. The slope of this line is -α and the y-intercept is a. The slope of the terminal segment is -β.
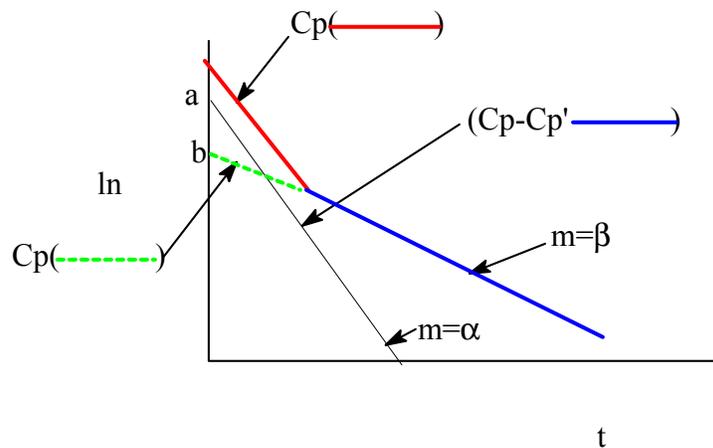

The initial concentration after an i.v. bolus dose can be given by:

$Cp0 = a + b$

Why is the slope so steep for the distribution phase of the Cp vs t curve?

Once a drug enters the body, elimination begins. After an i.v. bolus injection to the central compartment, there is distribution into the peripheral compartment and elimination from the central compartment. Thus, the concentration decreases rapidly at first. Distribution into the peripheral compartment continues until the free concentration in the central compartment (plasma) is equal to the free concentration in the peripheral compartment (tissue), i.e. there is a net flow of drug out of the plasma (along the concentration gradient) until steady-state is reached. In this situation, steady-state is not maintained and is only momentary.

After steady-state, a concentration gradient is again created - this time in the opposite direction - by the continual elimination of drug from the central compartment. In response to this, drug begins to flow back into the central compartment where it is eliminated. Thus, in the β-phase, the concentration of drug in the peripheral compartment is greater than that in the central compartment. The concentrations in both compartments decrease proportionally as elimination from the plasma continues. This may be viewed as a "pseudo steady-state": the body wants to reach an equilibrium between the amount of drug in each compartment (X_c and X_p for central and peripheral) but cannot due to elimination (k_{10}).
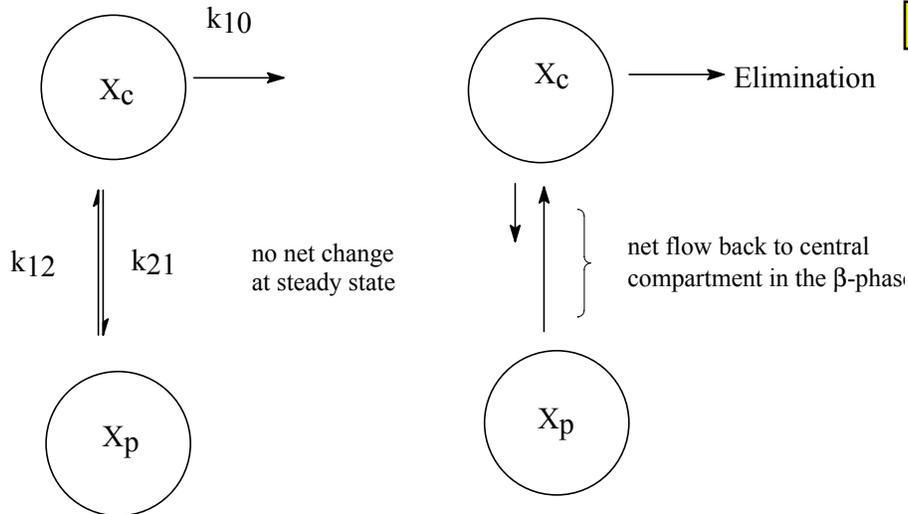
This "pseudo steady-state" in the β-phase may be apparent in comparing the concentration in the tissue to that in the plasma.
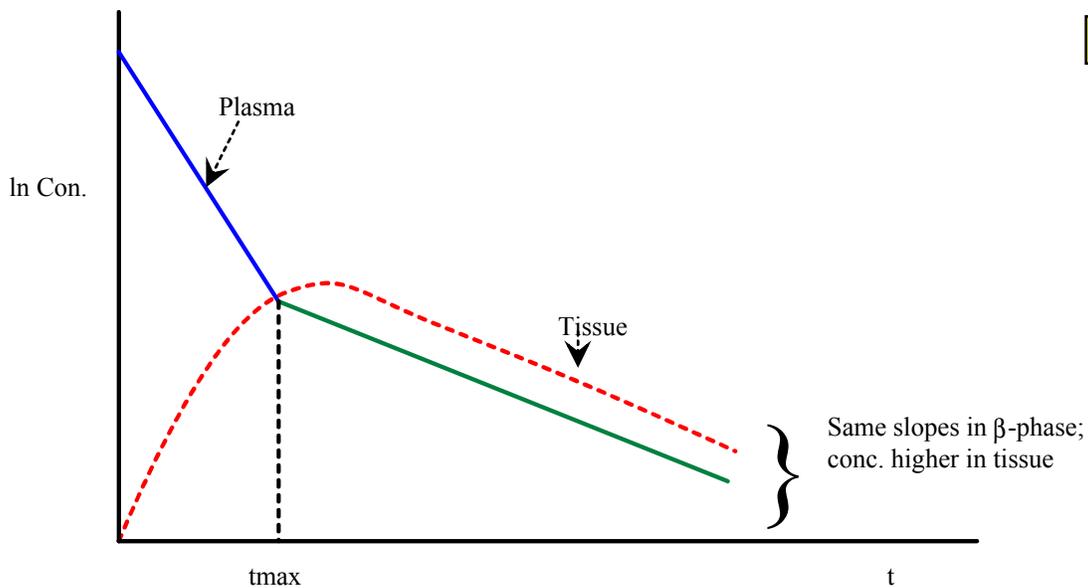
@ t_{max} the free concentration . In plasma is equal to the free concentration in the tissue. This is the steady-state.

Volume of distribution terms

Recall that V_d relates the amount of drug in the body to the concentration in the plasma. For a one-compartment model we saw an initial concentration of:

$$C_{p0} = \frac{D}{V_d}$$

which can be solved for V_d to give

$$V_d = \frac{D}{C_{p0}}$$

In the one compartment model there is a single V_d term (since we assumed immediate distribution and equilibrium). Thus, the amount of drug in the body at any time t, X_t, may be at time t, C_{pt} by a similar equation, $C_{p_t} = \dfrac{X_t}{V_d}$

V_d is the same whether we are interested in the initial concentration at t=0 or at later time points.

For a drug which requires sometime for distribution through the body (and, thus, fits a 2-compartment model), this is not the case. There will be different V_d terms depending on where we are in the C_p vs t profile. This is not as complicated as it may appear. Consider the initial plasma concentration for drug described by $C_p(t) = ae^{-\alpha t} + be^{-\beta t}$,

$$C_{p0} = \frac{D}{V_c}$$

Since the drug is only in the central compartment at time t=0 (i.e. no distribution has taken place yet), the volume term relating C_{p0} to dose is V_d, the volume of distribution of the central compartment. If we know the dose D and measure C_{p0}, we can calculate V_c,

$$V_c = \frac{D}{C_{p0}} = \frac{D}{a+b}$$

(substituting $C_{po} = a+ b$)

This term is useful if we want to predict initial (peak) plasma concentration following i.v. bolus dose. This will be valid only at t=0;. $C_{p0} = \dfrac{D}{V_c}$

Note: For a one compartment model, we expressed Cl_{TOT} in terms of a rate constant and V_d,

$$Cl_{TOT} = k_e \bullet V_d$$

In the 2 compartment model, we have several V_d terms to choose from in writing relationship like this. Since Cl_{TOT} and V_d are still independent (this fact has <u>not</u> changed), we must use different rate constants depending on the choice of V_d. Using V_c, we may write:

$$Cl_{TOT} = k_{10} \bullet V_c$$

where k_{10} is the elimination rate constant from the central compartment and V_c is the volume of distribution of the central compartment.

V_d after the initial time point (t=0_.

At any time point after t=0, V_d may vary. Thus, V_d will be a function of t, $V_d(t)$, just as we see for the amount of drug in the body, X_t, and the plasma concentration, C_{pt}.
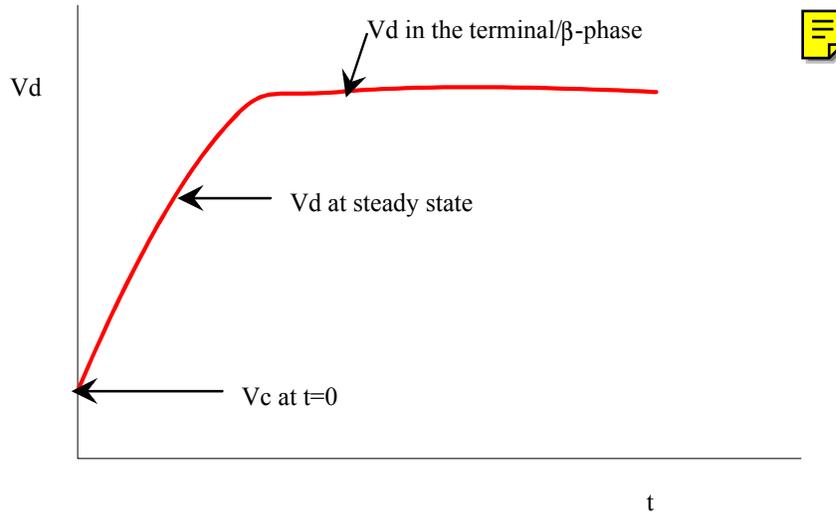
$$C_{p_t} = \frac{X_t}{V_{dt}} \quad \text{or} \quad V_{dt} = \frac{X_t}{C_{p_t}}$$

Although we can write an equation to determine V_d at any time point, it is not always practical to carry out these calculations (the equation includes AUC and AUC_t at the given time point). We can, however, determine Vd at two specific points without using the $V_d(t)$ equation. These are useful V_d terms that involve parameters already determined previously (e.g. α, β, etc.)

Vd at steady state

At steady-state, the free concentration in plasma is equal to the free concentration in the tissue. The V_d at this point, V_{dss}, is useful as it gives us the sum of the volume terms of the central and peripheral compartments at equilibrium. V_{dss} relates the amount of drug in the body at steady-state X_{ss}, to the plasma concentration, C_{pss},

$$. \; V_{dss} = \frac{X_{ss}}{C_{pss}} = V_c + V_p = \frac{a\beta^2 + b\alpha^2}{(a\beta + b\alpha)^2} \bullet D$$

The point of equilibrium is unique in that there is one overall elimination rate constant, ke, just as we saw in the one-compartment model. This k_e may be written in terms of the microconstants (k_{10}, k_{12}, k_{21}) used in the two compartment model.

This allows us to write

$$Cl_{TOT} = k_e \bullet V_{dss}$$

Vd in the β-phase.

Again, the Vd term in the β-phase (also referred to as the post-distribution or terminal phase) relates the amount of drug in the body to the plasma concentration.

$$V_{d\beta} = \frac{X_t}{C_{p_t}}$$

where t is some time point in the β-phase. This is a unique situation since the concentration of drug in the tissue is in a dynamic equilibrium with the plasma concentration ("pseudo steady-state"). Due to this dynamic equilibrium, X_t and C_{pt} decrease proportionally and V_{db} is constant (observe the equation above and the previous graphs. The Cl_{TOT} expression in the β-phase will involve the rate constant β,

$$Cl_{TOT} = \beta \bullet V_{d\beta}$$

Solving this equation for $V_{d\beta}$ gives

$$V_{d\beta} = \frac{Cl_{TOT}}{\beta}$$

Recall that Cl_{TOT} may be determined using a rather simple equation

$$Cl_{TOT} = \frac{D}{AUC_\infty} \text{ ,}$$

where D is the dose given and AUC_∞ is the total area under the curve (in the Cp vs t profile).

Substituting this into the equation for $V_{d\beta}$ gives

$$V_{d\beta} = \frac{D}{AUC_\infty \bullet \beta} \text{ .}$$

Since $V_{d\beta}$ may be calculated using the AUC, it is often called V_{darea},

$V_{d\beta} = V_{darea}$.

The choice of terminology may be based on the equation used to determine this Vd term.

There is one more V_d term that should be included in this discussion. Unlike the previous terms, however, this one has no physical meaning. It is merely an approximation and does not account for any distribution. This term is $V_{dextrap}$, so named because the calculation involves extrapolating the terminal slope back to the y-axis to find b,

The real $C_{po} = a + b$

Terminal Slope

m=-β

ln Cp

b

t
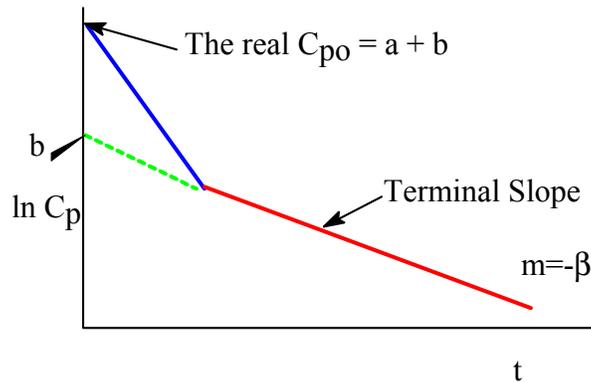
$V_{dextrap} = D/b$

$V_{dextrap}$ relates the concentration term b to the dose D at time t=0. Since the initial concentration is higher than b (Recall $Cp0 = a + b$), the calculation results in overestimating V_d.

In other words, $V_{dextrap}$ is calculated by pretending the Cp vs t profile fits a one-compartment model even though we know otherwise.

To summarize:

$$V_{dextrap} > V_{darea} > V_{dss} > V_c$$
$$\|$$
$$V_{d\beta}$$

Determining the loading dose

For an i.v. bolus injection, the initial plasma concentration may be predicted using

$$C_{p0} = \frac{D}{V_d} \ .$$

In a multiple dosing regimen, a loading dose can reduce the time needed to reach steady state levels. If we want to achieve $\overline{C}_{pss}$ without a delay,

$$\overline{C}_{pss} = \frac{LD}{V_d} \ ,$$

we need to be able to determine the loading dose.

$$\overline{C}_{pss} = \frac{LD}{V_d}$$

This equation may be solved for LD,

$$LD = \overline{C}_{pss} \bullet V_d \quad .$$

If we know the drug in question follows the Cp vs t profile of a two compartment model, which Vd term do we use to determine an appropriate loading dose?

V_c?   If V_c is used,

$$LD = \overline{C}_{pss} \bullet V_c$$

Since V_d is small and only involves the central compartment. Thus, our LD calculated will not be large enough.

$V_{dextrap}$? Since $V_{dextrap}$ is a gross overestimation of a meaningful V_d value, using it would result in a loading dose that is too big:

$$LD = \overline{C}_{pss} \bullet V_{dextrap} \quad .$$

This could lead to overshooting the range of the therapeutic window and result int oxic side effects.

V_{dss}? This is the best choice.

$$LD = \overline{C}_{pss} \bullet V_{dss}$$

If V_{dss} is not known, a value between $V_{d\beta}$ and V_c may be adequate.