Pharmacokinetic Calculations

Introduction. Pharmacokinetics involves the relationship between concentration of drug (and its metabolites), measured most often in plasma, drug dosage, and time. A vast majority of administered pharmaceutical agents are eliminated from the body by "linear pharmacokinetics". Strictly speaking, linear pharmacokinetics implies that the rate of drug elimination depends linearly on drug concentration ([drug]):

$$Rate_{elimination} = k * [drug] \quad (1),$$

where k is a proportionality constant that relates the [drug] to the rate of elimination.

However, to the clinician, linear pharmacokinetics also implies a number of additional, related properties. For example, a drug eliminated by linear pharmacokinetics has a constant half-life ($t_{1/2}$), defined as the amount of time required for measured drug concentration to be reduced by one-half (in the absence of any additional drug administration). Hence, if you observe that it required four hours for a drug to reduce from 4 to 2 µg/mL, then you know it will require another four hours to reduce from 2 to 1 µg/mL.

Probably the most valuable property of a drug eliminated by linear pharmacokinetics is the linear relationship between dosage and drug concentrations measured at specific times. For example, on a patient taking 100 mg of a drug orally every morning, you obtain a trough drug level of 2 µg/mL (a trough level is drawn just before their regular daily dosage and represents the lowest drug concentration within their dosage cycle). However, the drug requires a minimum trough level of 3 µg/mL to be effective. Because of linear pharmacokinetics, the correction is easy. To achieve a 50% increase in the trough drug level, you simply need to increase the prescribed dose by 50%. This is probably quite intuitive and, after a while, you will take it entirely for granted. However, what is important to appreciate is that with non-linear pharmacokinetics, this relation is NOT true. For a drug eliminated by non-linear pharmacokinetics, a 50% increase in drug dosage may result in an unexpectedly large increase in trough drug levels, which can be very dangerous. We will discuss this in more detail later, but I think you can appreciate how important linear pharmacokinetics is to clinicians monitoring drug therapy.

Drug Accumulation and Steady State. A drug eliminated by linear pharmacokinetics eventually reaches a limiting "steady state" drug concentration. Let's think about how this happens. Imagine a patient started on a constant intravenous (IV) infusion of a medication at a fixed rate ($Rate_{in}$). Initially, there is only a small amount of drug in their body and the corresponding plasma drug level is relatively low. Most likely, the associated rate of drug removal ($Rate_{out}$) is also low, as it is linearly proportional to the [drug]. Therefore, if the $Rate_{in} >> Rate_{out}$, then the amount of drug in the patient's body will continue to increase, along with the corresponding [drug] in plasma. This is the phase of drug accumulation in the body. As time passes, and the drug accumulates, the [drug] will slowly increase. Because of linear pharmacokinetics, the $Rate_{out}$ will also slowly increase (in a proportional manner). Eventually, the rate of drug removal will become equal to the rate of drug infusion ($Rate_{in} = Rate_{out}$) and the [drug] will become constant. This is called "steady state", which is another very beneficial property of linear pharmacokinetics. The expected [drug] at steady state ($[drug]_{SS}$) can be calculated easily, but we need to first define a few additional concepts.

The Two Rates. We will be talking about two different rates of drug elimination/removal from the body and it is very easy to get confused. I will be consistent and call one as the $Rate_{elimination}$ and the other as the $Rate_{out}$. Simply put, they differ only in their units. The $Rate_{elimination}$ describes how the [drug] decreases with time and hence has units of "concentration" divided by time (e.g. µg/mL/hr). The $Rate_{out}$ describes how the total amount of drug is removed from the body and has units of mass or moles of drug per unit of time (e.g. µg/hr).

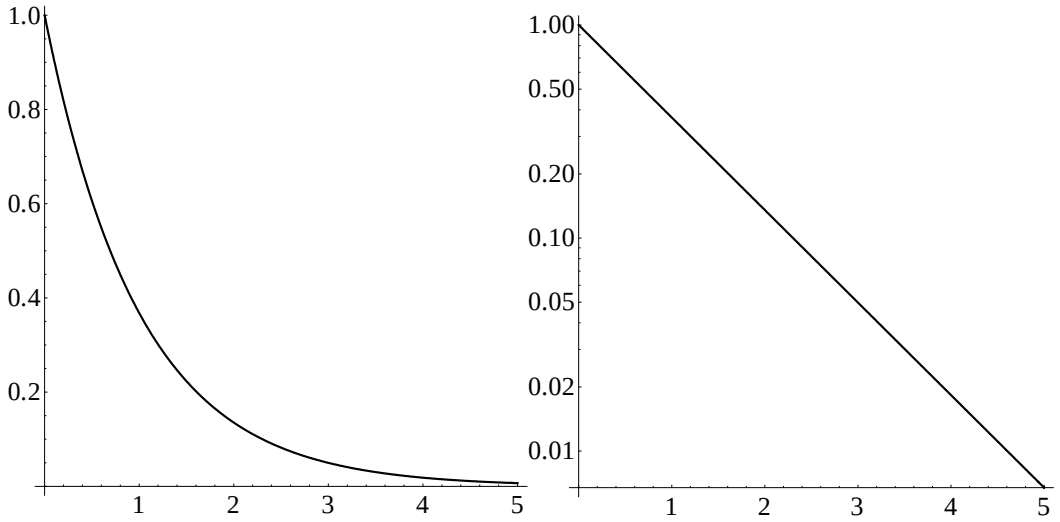
Exponential Decay. Returning to Equation 1 and remembering that the $Rate_{elimination}$ has units of "concentration" divided by time, it is apparent that the constant, k, has units of inverse time ($time^{-1}$). Equation 1 is a first-order, ordinary differential equation with a simple solution:

$$[drug]_t = [drug]_{t=0} e^{-kt} \quad (2)$$

$$[drug]_t = [drug]_{t=0} e^{\left(-\frac{-\ln 2}{t_{1/2}} t\right)} = [drug]_{t=0} 2^{\left(\frac{-t}{t_{1/2}}\right)} \quad (3)$$

Note that a negative sign has been introduced to emphasize that the [drug] is decreasing with time (k > 0). The second form of the equation simply recognizes that the rate constant, k, can be expressed in terms of the half-life, $t_{1/2}$. If you are watching a drug level decline with time, you will observe an exponential decay. This is illustrated below on the left.

Unfortunately, you will often see this decay plotted using a semi-log axis for [drug]. The result is that the decay of the [drug] follows a straight-line, shown on the right. This will confuse you at some point. Please remember that **linear pharmacokinetics results in an exponential decay of [drug] with time**, characterized by an exponential rate constant, k, or a constant half-life, $t_{1/2}$.



Volume of Distribution. Taking a break for a minute from drug elimination, we will now introduce the volume of distribution, V_d. The volume of distribution is a proportionality constant that relates the total amount of drug in someone's body to a measured drug concentration:

$$[drug] = \frac{amount\ of\ drug}{V_d} \quad (4).$$

When a drug is injected intravenously it is mixed into the blood volume, where it may bind to plasma proteins, bind to the surface of blood cells, and possibly be taken up into blood cells by either passive or active processes. The drug will also leave the bloodstream, permeating tissues to varying degrees, where it will also diffuse within fluid volumes, be taken up intracellularly, and bind to tissue components. This entire process is call ***drug distribution***. Assuming no ongoing drug elimination, an equilibrium state will eventually be reached where the drug is fully distributed and only a fraction of the original administered drug is present in the bloodstream (plasma). If at that point we measure the [drug] in plasma, we can relate it to the amount of drug administered to derive an ***apparent*** volume of water that contains all drug. A simplistic analogy is to consider a tub filled with water. If you carefully measured a quantity of drug, fully dissolved it in the tub of water, and then measured the [drug], skills you were taught in freshmen chemistry would allow you to calculate the volume of water in the tub (volume = amount of drug / [drug]). Now, imagine that a sponge was suspended in the tub of water and that sponge bound 90% of the drug you added. In this case, the measured [drug] in the "free" water would be tenfold lower than before. If you did not take into consideration the effect of the sponge and calculated the water volume, the derived value would be tenfold higher. Instead of representing the true volume of water in the tub, it would represent an apparent volume of water required to hold all the drug. In analogous fashion, pharmacokinetic volumes of distribution represent apparent volumes of aqueous solution that would be required to dissolve all the administered drug. They are often much larger than the actual fluid volume containing the drug, owing to extensive binding of the drugs to proteins and other tissue components.

The most common clinical use for the volume of distribution (V_d) is the calculation of "peak" drug levels after an intravenous injection. If we assume that distribution of the drug throughout the body is rapid and that drug elimination during this period is insignificant, the [drug] measured soon after administration can be calculated:

$$[drug]_{peak} = \frac{dose_{bolus}}{V_d} \quad (5).$$

Clearance. This one tends to be a little tricky to fully understand, though it is actually quite simple. Clearance is a rate with units of "volume per time" and represents the volume of measured fluid that appears to be completely cleared of the drug over a unit of time. Please allow me to return to the simplistic analogy involving the tub of water with dissolved drug. If you were to remove one liter of water from that tub, meticulously removed every drug molecule from that one

liter, and then returned the now drug-free liter of water back to the tub, then you would have ***cleared*** one liter of the tub from drug. The amount of drug removed from the tub would be simply one liter multiplied by the original [drug]. Of course, because you returned the drug-free liter of water back to the tub, the [drug] in the tub would now decrease. If you were to repeat the process, you would again clear one liter of the drug, but the total amount of drug you removed would be slightly less, as the [drug] was slightly lower. If you continued to repeat this process over and over, and each cycle took one hour to perform, the drug ***clearance*** would be 1 liter/hour. Notice how this process is naturally linear or first-order, as the rate of drug removal is directly proportional to the [drug]. In fact,

$$Rate_{out} = Clearance * [drug] \quad (6).$$

It is important to remember that constant clearance is a property of linear kinetics. Any drug eliminated by linear pharmacokinetics will be characterized by a constant clearance. Similarly, any drug observed to maintain a constant clearance will be eliminated by linear pharmacokinetics. In contrast, drugs cleared by zero-order (nonlinear) pharmacokinetics will not be characterized by a constant clearance; instead, the *apparent* clearance will vary with [drug]. Thus, in the absence of first-order kinetics, the concept of clearance is neither useful nor appropriate.

Now imagine a drug that is cleared entirely by the kidneys in a patient with a glomerular filtration rate (GFR) of 100 mL/min. If the drug is neither reabsorbed nor secreted in the renal tubules, then the clearance of the drug is also 100 mL/min. If 50% of the drug is reabsorbed, then the clearance is simply 50 mL/min. In truth, there is not such a clean relation between a physiologic behavior and clearance for most drugs. Similar to volume of distribution, it is best to consider clearance as the *apparent* volume of plasma (i.e. the measured fluid) that is completely cleared of the drug per unit time. As long as you know that the drug is eliminated by first-order pharmacokinetics across the relevant range of drug concentrations, then you can characterize drug removal in terms of a constant clearance.

Revisiting the Two Rates. You are now equipped with definitions for the two rates, one for "elimination" with units of drug concentration per unit time, and the other for "removal" with units of an amount of drug per unit time. How do they relate? The answer is the volume of distribution, as it is the V_d that is actually being cleared. If you know that, at one point in time, 1 mg of drug is being removed from the body per hour (a $Rate_{out}$), how would you calculate how much the [drug] is decreasing with time? The answer is easy; you would divide the amount of drug removed per time by the total volume of the solution to get the change in concentration per unit time, and this volume is simply V_d. Hence,

$$Rate_{elimination} = \frac{Rate_{out}}{V_d} \quad (7) \; and$$

$$Clearance = k * V_d \quad (8).$$

If you get confused with all these relations, always try to work out the units. You can usually remember the units for a subset of terms, and then the rest just fall into place.

Steady State Drug Levels. We can now calculate the concentration of drug at steady state, $[drug]_{steady\ state}$. Remember that steady state occurs when the rate of drug removal is the same as the rate of drug administration ($Rate_{in} = Rate_{out}$). As well, the rate of drug removal ($Rate_{out}$) is simply the clearance times the [drug]. Hence,

$$[drug]_{steady\ state} = \frac{Rate_{in}}{Clearance} \quad (9).$$

Clinically, the above equation is used to determine the eventual, continuous drug concentration in a patient receiving an intravenous drug infusion. As discussed previously, the patient does not reach the $[drug]_{steady\ state}$ immediately after the start of the infusion. The drug must first accumulate in the body until the steady state condition is met. The length of time required is determined by the half-life, which is explored in more detail below.

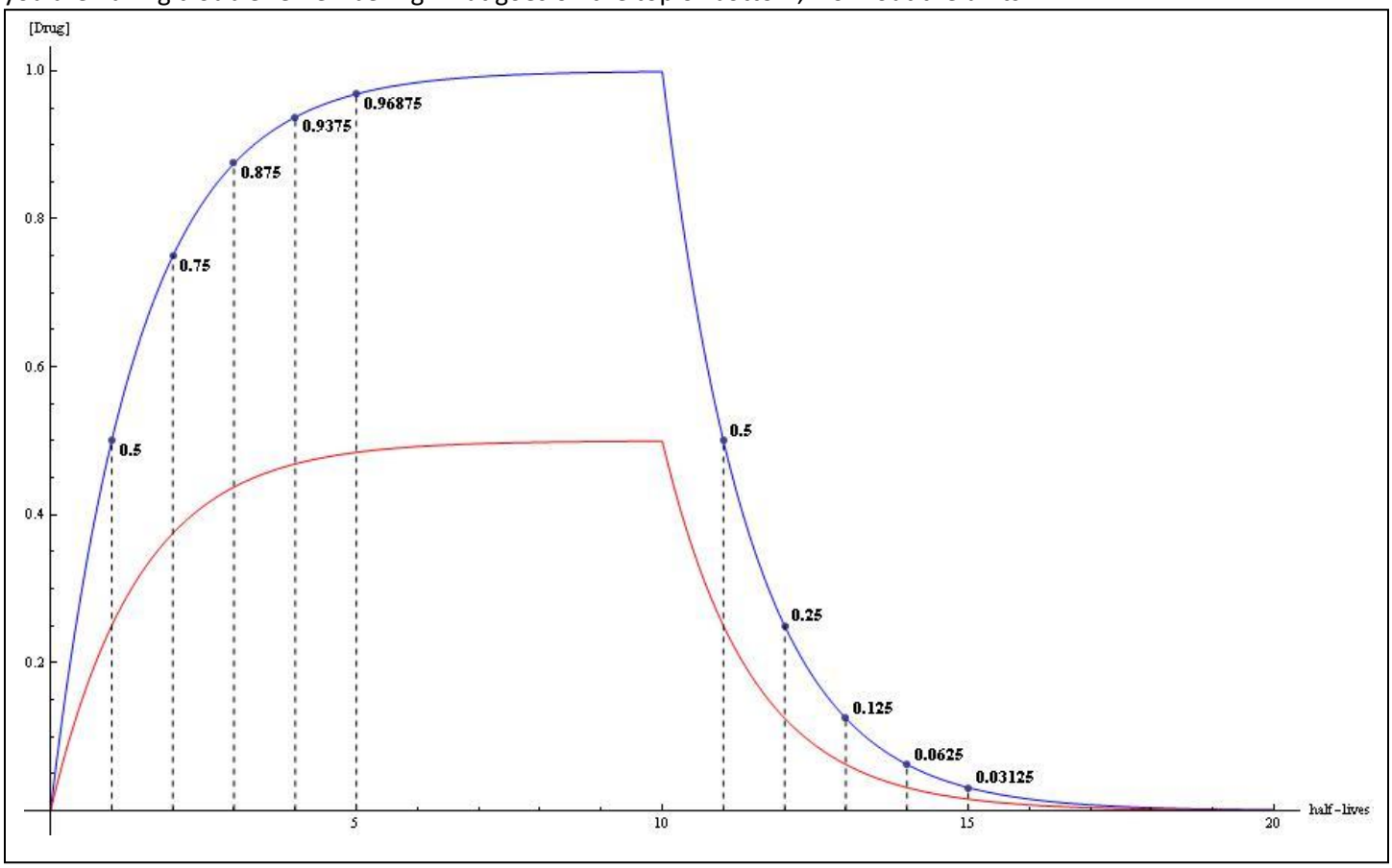
Drug Half-Life. Knowledge of a drug's half-life is clinically valuable. Half-life determines the length of time required to reach steady state after starting a new drug, after a change in dosage, after stopping the drug, or after a change in drug clearance. Any transition to a new steady state requires the same amount of time. After one half-life, the transition from the previous value to the new steady state will be 50% complete. After two half-lives, 75% complete. After three half-lives, 87.5%, etc. Over five half-lives are required for the transition to be >97% complete. Oftentimes, it is not practical clinically to wait for the full five half-lives to recheck a patient's drug level after a change in dosage, three half-lives is a common compromise as the transition should be about 90% complete. However, the problem really isn't how long to wait to measure a new drug level, but remembering to consider the likely number of half-lives elapsed in the interim.

Many drugs have short half-lives (<= 8 hours), such that measuring drug levels daily and making dosage adjustments accordingly works well, as three half-lives are likely to elapse between blood draws. Difficulties arise with half-lives of 12 – 24 hours or more. If the clinician is not careful, they can end up "chasing their tail" making dosage adjustments too frequently. This situation is complicated by the pressures to reduce length of hospital stay and prevent readmission.

A drug's half-life is determined by its volume of distribution and its clearance. It is important to remember that V_d and clearance are the more "fundamental" pharmacokinetic concepts, from which a drug's half-life ($t_{1/2}$) can be derived:

$$t_{1/2} = \frac{\ln(2) * V_d}{Clearance} \cong \frac{0.693 * V_d}{Clearance} \quad (10).$$

I hope it is apparent that an isolated change in either V_d or clearance will have either a direct or inversely proportionate effect on $t_{1/2}$. This equation is worth remembering as it is my experience that one can usually find a drug's V_d and either its $t_{1/2}$ or its clearance, but rarely all three. Depending on what you need, you may need to calculate the third. Again, if you are having trouble remembering what goes on the top or bottom, work out the units.



Review of Important Features of Linear Pharmacokinetics.

1. Rate of drug elimination/removal is proportional to serum drug concentration.
2. Drug elimination follows an exponential decay with time.
3. Drug elimination can be characterized by a constant half-life.
4. Drug elimination can be characterized by a constant clearance.
5. During continuous administration, there is an initial drug *accumulation* phase followed by a limiting *steady-state* drug concentration.
6. There is a directly proportional relationship between dose and corresponding steady-state drug concentrations (or trough/peak drug levels with intermittent dosing).

Critical equations/concepts worth memorizing.

1. Relationship between V_d and drug concentration in plasma: $[drug]_{plasma}$ = {amount of drug in body}/V_d. This relationship allows one to calculate the increase in plasma drug concentration after a quantity of drug is administered to a patient, assuming rapid absorption and distribution, commonly referred to as a ***peak*** drug level (see Equation 5).
2. At steady-state, $Rate_{in} = Rate_{out}$. The rate of drug administration is equal to the rate of elimination. This allows calculation of the plasma drug concentration at ***steady state***: $[drug]_{steady\text{-}state} = Rate_{in}/Cl$ (see Equation 9).
3. Knowing a drug's ***half-life*** ($t_{1/2}$) is clinically valuable and can be calculated from the more fundamental pharmacokinetic parameters, V_d and Cl: $t_{1/2} = 0.693 * V_d / Cl$ (see Equation 10).

Important deviations from the simple model.

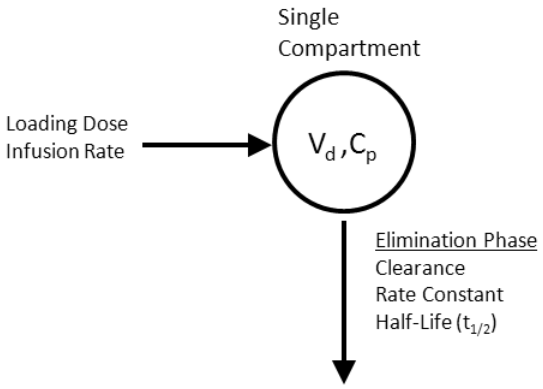
1. Drug absorption/resorption.
2. Drug distribution/redistribution (two-compartment pharmacokinetics).
3. Non-linear or Zero-order (i.e. saturation) pharmacokinetics.

In order to aid with visualization, we have prepared a number of online pharmacokinetic simulators for you to explore. One is maintained by the Teaching and Learning Center at the Yale School of Medicine (Gary Leydon) and can be found at http://curriculum.med.yale.edu/pharm/calc/ and has been optimized for the iPad. Alternatively, if you are using a Mac or PC, you can use the simulators I prepared at http://hodsdon.com/PK. The latter were programmed in Mathematica™ and require the free CDF Player/Plugin available from Wolfram (www.wolfram.com). Upon clicking on one of the models, you will be directed to the appropriate download page. I have also prepared a brief manual on how to use the controls for the Mathematica™ simulators: http://hodsdon.com/PK/manual.pdf.

In the following section, I will provide a more detailed description of each of the simulators. For completeness, I include the detailed equations utilized by each pharmacokinetic model, although no one should be worried about memorizing them, understanding their derivation, or even ever doing direct calculations. The primary goal is to utilize the simulators to visualize the general concepts that will be useful during patient management.

Model 1: Continuous Infusion

This first pharmacokinetic model simulates plasma drug levels during a continuous intravenous infusion. Note that in these simulations the units of concentration and time displayed on the two axes are NOT shown. They are meant to be arbitrary and to represent whatever units the user wishes. Hence, drug concentrations could be in mg/L or µM and time could be seconds or hours. However, it is critical that the user keeps units consistent between all the input parameters. If the intention is for drug concentrations to be expressed in mg/L and elapsed time in hours, drug dosage must also be expressed in mg (or mg/hour in the case of an infusion rate), volumes of distribution must be in liters, and clearance expressed as L/hour.



In the simulation, the user controls the infusion rate (k_{in}), in units of drug concentration per time, the total length of the infusion (t_{inf}) and an optional decay time (t_{decay}) after the infusion is stopped. The only relevant pharmacokinetic parameters are volume of distribution (V_d or V_f) and clearance (Cl). This model should be useful to observe the fundamental properties of linear pharmacokinetics. As the patient begins with no drug in their system (assuming load = 0), at the very beginning of the infusion, drug concentration is zero. As the drug is infused, concentration steadily increases until steady state is achieved, where $rate_{in} = rate_{out}$ ($k_{in} = k_{out}$) and the drug concentration remains constant at its steady state value:

$$C_{p,steady\ state} = \frac{k_{in}}{Cl} \quad (11).$$

The rate of accumulation is controlled by the drug's half-life, $t_{1/2}$, which can be calculated from the elimination rate constant, k_e:

$$k_e = \frac{Cl}{V_d} \quad (12),$$

$$t_{\frac{1}{2},e} = \frac{\ln(2)}{k_e} \quad (13).$$

The plasma drug concentration at any given time is calculated:

$$If\ t \leq t_{inf},\quad C_p = \frac{k_{in}\left(1 - e^{-k_e t}\right)}{V_d k_e} + \frac{load * e^{-k_e t}}{V_d} \quad (14),$$

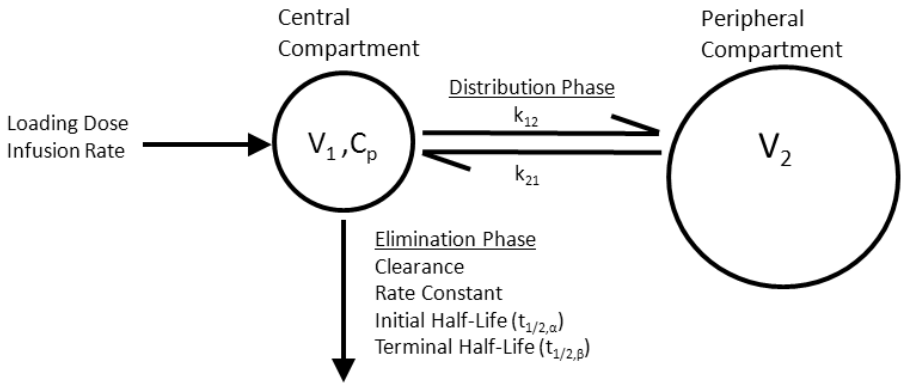
$$If\ t > t_{inf},\quad C_p = \frac{k_{in}\left(1 - e^{-k_e t_{inf}}\right)e^{-k_e\left(t - t_{inf}\right)}}{V_d k_e} + \frac{load * e^{-k_e t}}{V_d} \quad (15).$$

The model includes an optional initial loading dose, assumed to be administered instantaneously at time = 0. The loading dose can be used to bring the drug concentration instantaneously up to the desired level according to

$$C_{p,bolus} = \frac{load}{V_d} \quad (16).$$

Set to their default values of $k_{in} = 1$, load = 0, $V_d = 1$, and Cl = 0.1, a steady state drug concentration of 10 (in relative units) is achieved after ~ 5 half-lives ($t_{1/2e}$ ~ 6.9), or around 35 hours. Instead of waiting that long, a loading dose of 10 could be applied initially to bring the patient immediately up to the desired concentration. After the loading dose is administered, an infusion rate of 1 is used to "maintain" the desired steady state level, which is often referred to as the "maintenance dose".

Model 2: Continuous Infusion with Drug Distribution (two-compartment)



In the second pharmacokinetic model, we consider a continuous intravenous infusion of a drug that distributes slowly from a central compartment (with volume V_1) into a peripheral compartment (with volume V_2). The patient's bloodstream is contained within the central compartment and, thus, provides the pathways for drug administration and elimination, as well as, the sampling site for measuring plasma drug concentrations (C_p). A simple, easily visualized example would be a drug that initially dissolves into the extracellular fluid volume, representing the central compartment, and then slowly diffusing across cell membranes into intracellular fluid, representing the peripheral compartment. In this case, V_1 would equal the extracellular fluid volume and V_2 would equal the intracellular fluid volume. After distribution is complete, the total volume of distribution, V_f, would be equal to the sum of V_1 and V_2, which in this case is the total body fluid volume.

Note that in the simulation the user controls the final volume of distribution, V_f, and the fractional initial volume, V_iF:

$$V_i = V_1 = V_iF * V_f \quad (17).$$

The kinetics of drug distribution and redistribution between the two compartments are controlled by two, first-order rate constants, k_{12} and k_{21}. However, these values are not very intuitive and difficult to relate to the observed behavior of C_p versus time. As an alternative, we can consider an *effective* half-life for distribution, $t_{1/2,d}$, defined solely by the k_{12} rate constant controlling distribution of drug from the central compartment to the peripheral compartment:

$$t_{\frac{1}{2},d} = \frac{\ln(2)}{k_{12}} \quad (18).$$

This parameter abstractly represents the first-order kinetic process for diffusion of the drug from the central to the peripheral compartment after an instantaneous loading dose when both drug elimination (k_e) and redistribution (k_{21}) are non-existent (or in the approximation, insignificant). In reality, drug administration, elimination, distribution and redistribution are ongoing simultaneously and a truly isolated distribution phase is not really observed. Nevertheless, the $t_{1/2,d}$ is a more useful and intuitive way of discussing distribution/redistribution kinetics and what is directly controllable by the user in the simulation.

The equations for calculating C_p as a function of time are more complicated:

$$t \leq t_{inf}: C_p = \frac{k_{in}}{V_1}\left(\frac{(\alpha - k_{21})(1 - e^{-\alpha t})}{\alpha(\alpha - \beta)} + \frac{(k_{21} - \beta)(1 - e^{-\beta t})}{\beta(\alpha - \beta)}\right) + \frac{load}{V_1}\left(\frac{(\alpha - k_{21})e^{-\alpha t}}{(\alpha - \beta)} + \frac{(k_{21} - \beta)e^{-\beta t}}{(\alpha - \beta)}\right) \quad (19),$$

$$t > t_{inf}: C_p = \frac{k_{in}}{V_1}\left(\frac{(\alpha - k_{21})(1 - e^{-\alpha t_{inf}})e^{-\alpha(t - t_{inf})}}{\alpha(\alpha - \beta)} + \frac{(k_{21} - \beta)(1 - e^{-\beta t_{inf}})e^{-\beta(t - t_{inf})}}{\beta(\alpha - \beta)}\right)$$
$$+ \frac{load}{V_1}\left(\frac{(\alpha - k_{21})e^{-\alpha t}}{(\alpha - \beta)} + \frac{(k_{21} - \beta)e^{-\beta t}}{(\alpha - \beta)}\right) \quad (20).$$

Note that relevant rate constants k_{12}, k_{21}, α, and β are calculated (with k_e as in Equation 12):

$$k_{12} = \ln(2)/t_{1/2,d} \quad (21),$$

$$k_{21} = k_{12}(V_1/V_2) \quad (22),$$

$$\alpha = \frac{(k_e + k_{12} + k_{21}) + \sqrt{(k_e + k_{12} + k_{21})^2 - 4k_e k_{21}}}{2} \quad (23),$$

$$\beta = \frac{(k_e + k_{12} + k_{21}) - \sqrt{(k_e + k_{12} + k_{21})^2 - 4k_e k_{21}}}{2} \quad (24).$$

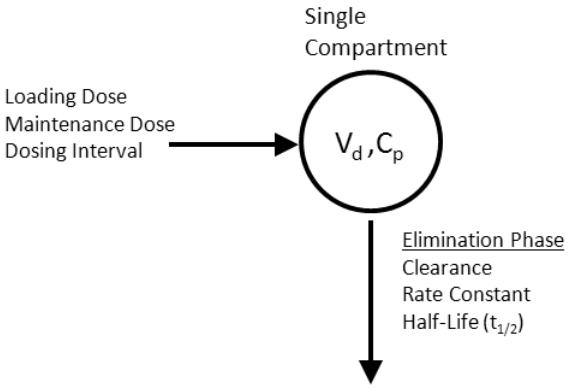
In this model, the simulated curves are effectively the sums of two exponentials represented by the new rate constants, α and β. The initial part of the decay (or the accumulation) phase is dominated by α and the terminal phase is dominated by β. To associate these curves with intuitive values, corresponding half-lives are defined:

$$t_{\frac{1}{2},\alpha} = \frac{\ln(2)}{\alpha} \quad (25),$$

$$t_{\frac{1}{2},\beta} = \frac{\ln(2)}{\beta} \quad (26).$$

Model 3: Intermittent Dosing

In the third pharmacokinetic model, we simulate intermittent dosing of a medication at specified intervals (τ). Most often this represents oral administration of a drug, which can be given daily/q.d. (τ=24 hrs), twice daily/b.i.d. (τ=12 hrs), thrice daily/t.i.d. (τ=8 hrs), etc. Absorption and distribution are considered to be instantaneous. This model could also simulate intermittent intravenous injections with instantaneous distribution. The user is able to control the number of doses given to the patient ("total doses"), whether the first dose constitutes an optional loading dose ("load"), the dosing interval ("tau"), the maintenance dose ("dose") and the bioavailability ("F"). Pharmacokinetic parameters for the patient include volume of distribution (V_d) and clearance (Cl).



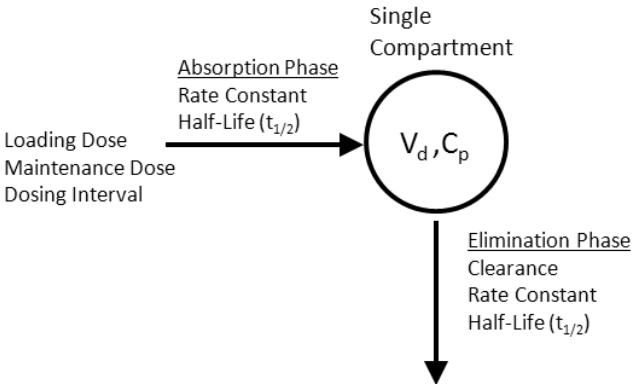
In order to calculate C_p versus time (t), the model calculates the total number of administered doses (n) and the time accumulated since the last dose was administered (t_e). The rate constant for elimination, k_e, and its corresponding half-life, $t_{1/2,e}$, continues to be calculated according to Equations 12 and 13, respectively:

$$C_p = \frac{F * dose}{V_d} \frac{\left(1 - e^{-nk_e\tau}\right)}{\left(1 - e^{-k_e\tau}\right)} e^{-k_e t_e} + \frac{F * load}{V_d} e^{-k_e t} \quad (27).$$

Model 4: Intermittent Dosing with Absorption

Here, intermittent dosing is combined with first-order absorption kinetics (most common). Distribution is considered to be instantaneous. This model could be used for oral dosing or intermittent subcutaneous or intramuscular injections. Parameters are identical to Model 3 (intermittent dosing alone) with the addition of a half-life for absorption ($t_{1/2,a}$). Similar to other half-lives, an exponential rate constant for absorption is calculated:

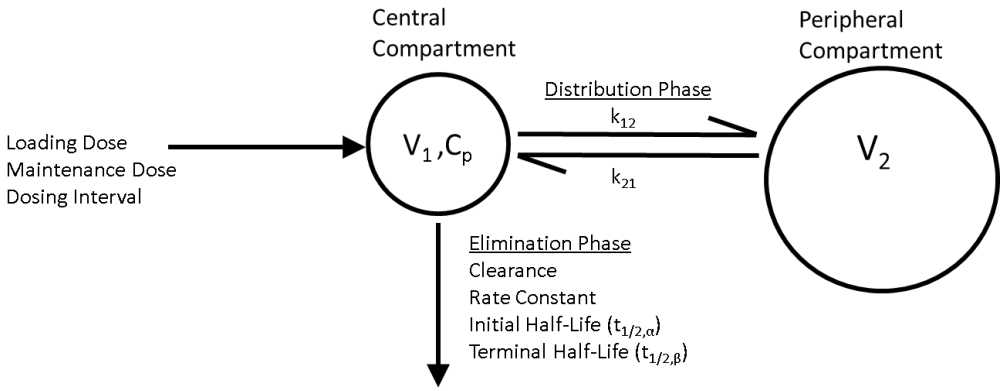
$$k_a = \ln(2)/t_{1/2,a} \quad (28).$$



Plasma drug concentrations as a function of time are calculated:

$$C_p = \frac{F * dose * k_a}{V_d(k_a - k_e)} \left(\frac{\left(1 - e^{-nk_e\tau}\right)}{\left(1 - e^{-k_e\tau}\right)} e^{-k_e t_e} - \frac{\left(1 - e^{-nk_a\tau}\right)}{\left(1 - e^{-k_a\tau}\right)} e^{-k_a t_e} \right) + \frac{F * load * k_a}{V_d(k_a - k_e)} \left(e^{-k_e t} - e^{-k_a t}\right) \quad (29).$$

Model 5: Intermittent Dosing with Distribution Phase (two-compartment)



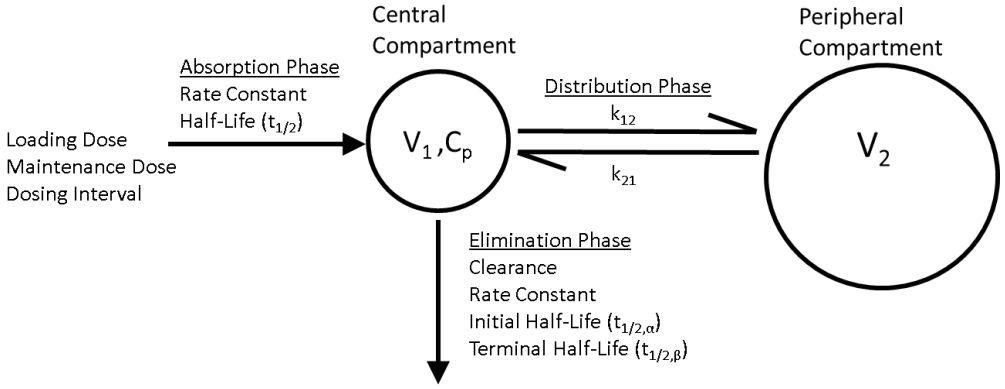
Here, intermittent dosing is combined with a distribution phase. Absorption is considered to be instantaneous. This is not a common scenario, clinically. However, it should serve to illustrate the isolated effects of distribution phase. Again, parameters are identical to Model 3 (Intermittent Dosing), with the addition of all the two-compartment kinetic parameters and volumes detailed above for Model 2 (Continuous Infusion with Distribution Phase). The initial volume of distribution is V_i, which is the same as V_1. In the model V_i is calculated as a fraction of the final volume of distribution, V_f, using the adjustable parameter, V_iF (see Equation 17). The final volume of distribution, V_f, is the sum of the two compartment volumes, V_1 and V_2. Instead of directly specifying k_{12} and k_{21}, we define an *effective* half-life for distribution, $t_{1/2,d}$, defined solely by the k_{12} rate constant controlling distribution of drug from the central compartment to the peripheral compartment (see Equation 18).

Plasma drug concentrations (Cp) as a function of time (t) are calculated:

$$C_p = \frac{F * dose}{V_1}\left(\frac{(\alpha - k_{21})}{(\alpha-\beta)}\frac{(1-e^{-n\alpha\tau})}{(1-e^{-\alpha\tau})}e^{-\alpha t_s} + \frac{(k_{21}-\beta)}{(\alpha-\beta)}\frac{(1-e^{-n\beta\tau})}{(1-e^{-\beta\tau})}e^{-\beta t_s}\right) + \frac{F * load}{V_1}\left(\frac{(\alpha - k_{21})}{(\alpha-\beta)}e^{-\alpha t} + \frac{(k_{21}-\beta)}{(\alpha-\beta)}e^{-\beta t}\right) \quad (30)$$

Again, a bi-exponential decay curve is expected with rate constants α and β, defined by Equations 21 – 24.

Model 6: Intermittent Dosing with both Absorption and Distribution Phases (two-compartment)



In the final and most complex model, intermittent dosing is combined with both absorption and distribution phases. This is a common clinical scenario. All relevant pharmacokinetic parameters are detailed above in the previous models. If you can understand Models 3 – 5, then you understand this one. There is nothing new here.

Plasma drug concentrations (Cp) as a function of time (t) are calculated:

$$C_p = \frac{F * dose}{V_1}\left(\frac{(\alpha - k_{21})e^{-\alpha t_s}}{(\alpha-\beta)(k_a-\alpha)}\frac{(1-e^{-n\alpha\tau})}{(1-e^{-\alpha\tau})} + \frac{(k_{21}-\beta)e^{-\beta t_s}}{(\alpha-\beta)(k_a-\beta)}\frac{(1-e^{-n\beta\tau})}{(1-e^{-\beta\tau})} + \frac{(k_{21}-k_a)e^{-k_a t_s}}{(k_a-\alpha)(k_a-\beta)}\frac{(1-e^{-nk_a\tau})}{(1-e^{-k_a\tau})}\right) + \frac{F * load}{V_1}\left(\frac{(\alpha - k_{21})e^{-\alpha t}}{(\alpha-\beta)(k_a-\alpha)} + \frac{(k_{21}-\beta)e^{-\beta t}}{(\alpha-\beta)(k_a-\beta)} + \frac{(k_{21}-k_a)e^{-k_a t}}{(k_a-\alpha)(k_a-\beta)}\right) \quad (31)$$

Model 1: Case Example (Continuous IV theophylline infusion)

A patient requires a continuous IV infusion of theophylline to prevent bronchoconstriction. The desired plasma concentration is 15 mg/L. Theophylline has an average half-life of 4 hours and volume of distribution of 25 liters. Calculate the appropriate maintenance dose to maintain a steady-state level of 15 mg/L.

First, you need to estimate clearance using $Cl = 0.693 * Vd / t_{1/2} = 0.693 * 25\ L / 4\ hours = 4.3\ L/hr$.

Now, it is easy to calculate the desired infusion rate: $rate_{in} = [drug]_{ss} * Cl = 15\ mg/L * 4.3\ L/hr = 64.5\ mg/hr$.

You can simulate the patient's plasma drug concentration over time using the Pharmacokinetic Simulator (http://curriculum.med.yale.edu/pharm/calc/). Alternatively, if you are using a Mac or PC, you can use the simulators I prepared at (http://hodsdon.com/PK); however, you will need to install the free CDF Player/Plugin from Wolfram (www.wolfram.com). Under "Select Calculator" choose "Continuous Infusion". Change Vf, Cl and Ir (Infusion Rate) to the appropriate values and you should see that the limiting [drug] ~ 15 mg/L.

Now, if you can't wait the ~ 12 hours for the drug to accumulate in the patient's body and start to approach the steady state value, you can give a loading dose. Normally these are given over some short duration of time (e.g. 30 minutes). However, here, we are going to assume the loading dose is given instantaneously. Calculate the necessary loading dose to immediately reach a [drug] ~ 15 mg/L.

This is simple. Use "loading dose" = [drug] * Vd = 15 mg/L * 25 L = 375 mg.

Go back to the Pharmacokinetic Simulator and change load to 375.

This example uses all three of the fundamental equations that I recommend you memorize.

Model 2: Case Example (IV administration of thiopental)

A patient is given 300 mg of thiopental to induce anesthesia (along with a paralyzing agent), rapidly intubated, and started on halothane gas to maintain anesthesia. If the halothane gas was not started, how long before the patient "wakes up"? For the purpose of this case, we can assume that thiopental is adequately modeled using a two compartment pharmacokinetic model (i.e. linear pharmacokinetics with a distribution phase) and that unconsciousness is induced at a plasma concentration > 5 mg/L, although in reality the situation is slightly more complex. The final (total) volume of distribution for thiopental in this patient is 175 L and the elimination clearance is 7 L/hour. However, upon IV administration, thiopental immediately distributes into an initial volume that is 20% of the final volume, which subsequently distributes into the total volume of distribution with a half-life of ~0.7 hours.

Program all of the above into Model 2 (continuous infusion with distribution phase). Note that you should use a loading dose of 300 mg, but set both the infusion rate and infusion interval to zero. What you should observe is that the patient's drug concentration shoots above 5 mg/L instantaneously, inducing unconsciousness, and rapidly decrease during distribution phase. Within 30 minutes, the level has fallen below 5 mg/L and the patient will wake up. However, note that nearly all the administered drug is still in the patient's body and will be slowly eliminated with a half-life of around 20 hours. Thus, thiopental is considered to be a short acting agent due to its rapid distribution phase; it is actually eliminated much more slowly.

Compare this to a steady state infusion of thiopental at 60 mg/hour. To do this, simply reduce the loading dose to zero and increase the infusion rate to 60. You also need to increase the infusion interval to something long, like 120 hours. Infusions like this are done in the ICU to reduce intracranial pressure. The [drug] at steady state is around 8.6 mg/L, which is the same as the peak [drug] in the above example of a single IV bolus to induce anesthesia. However, notice that when the infusion is stopped, around 12 hours are now required for the [drug] to fall below 5 mg/L. During the prolonged infusion, thiopental "saturated" the peripheral compartment, raising its concentration to 8.6 mg/L as well. Hence, after terminating the infusion, the decline in drug concentration becomes dependent on the elimination half-life.

Model 3: Case Example (Intermittent IV theophylline administration)

Let us revisit the patient in the first example who is on a steady state infusion of theophylline. Although you wouldn't really want to do this, let us try and devise an intermittent dosing schedule where the patient is given IV bolus injections of the drug every few hours (we imagine that the infusion pump is broken and we must resort to intermittent IV injections). The therapeutic range for theophylline is 10 – 20 mg/L. We would like an average steady state value of 15 mg/L with peaks below 20 mg/L and troughs above 10 mg/L. We know that 64.5 mg/hr infusion provides a steady state of 15 mg/L. So, what if we just did injections of that amount every hour? Try to simulate this.

You should have observed that after steady state is achieved, which takes almost a day, the patient starts to oscillate between ~ 13.7 and 16.2 mg/L, keeping them well within the therapeutic range. But, this is a demanding schedule for the staff, as they have a lot of patients, so we now want to see how much we can reduce the frequency of injections. Try simulating injection of 2*64.5 mg every 2 hours, or 3*64.5 mg every 3 hours, 4*64.5 mg every 4 hours, etc. – up to a dosing interval of 6 hours.

You should have observed that the largest dosing interval that can be tolerated without the patient "peaking" over 20 mg/L or dropping below 10 mg/L is about 4 hours (with doses of 258 mg). This becomes very important when we consider prescribing theophylline pills to be taken by mouth (PO) in an outpatient setting. If you ask an asthmatic child to take 3 x 500 mg pills per day (each every 8 hours), what will happen? Note that the oral bioavailability of theophylline pills is 100% (or 1.0).

Ouch. Peaks are over 25 mg/L and troughs are close to 5 mg/L. This will not work. However, we aren't properly considering the effect of absorption. For that let's go to the next pharmacokinetic model: intermittent dosing with delayed absorption (Model 4).

Model 4: Case Example (Intermittent PO theophylline administration)

Okay, still on the same patient, all the inputs to the model should be the same except now we can select an absorption half-life. An uncoated theophylline tablet is absorbed quickly with a half-life no longer than 15 minutes. Enter this in the model as 0.25 hours. Although peaks are still over 20 mg/L and troughs are below 10 mg/L, they are blunted relative to the previous model that did not consider absorption kinetics. Taking the pills with food slows down absorption even more, with half-lives between 0.5 and 1 hour, depending on fat content of the meal. Lastly, extended release tablets are absorbed even slower, with effective half-lives of 2 – 4 hours. These are typically administered every 12 hours (twice per day). Look at the effect of 750 mg dosing twice per day with a four hour absorption half-life. Note that sustained-release and extended-release formulations are not always absorbed with linear/first-order kinetics (i.e. an exponential increase). Ideally, they would release a fixed amount per hour thereby approximating a continuous infusion. In reality, their absorption kinetics are probably more complex and show properties of both first-order and zero-order kinetics.

Model 5: Case Example (Intermittent IV digoxin administration)

For this pharmacokinetic model, which includes intermittent dosing and a distribution phase (but not absorption), we will consider daily IV injections of digoxin. The pharmacokinetics of digoxin are complicated. Both the volume of distribution and the elimination clearance depend on a patient's glomerular filtration rate. Additionally, digoxin has a narrow therapeutic range (0.5 – 2.0 µg/L depending on the clinical utility), which makes it very difficult to dose. There are many formulas to guide digoxin dosing and to predict pharmacokinetic parameters. We are going to use

$$V_f(L) = 3.8(Body\ weight\ in\ kg) + 3.1(Cl_{Cr} as\ mL/\text{min})$$

$$Cl\left(\frac{mL}{min}\right) = 0.8(Body\ weight\ in\ kg) + (Cl_{Cr} as\ mL/\text{min}) l(L/hour) = (Cl\ mL/min)(60\ min/hour)/(1000\ mL/L)$$

Our patient weighs 80 kg and you have estimated their creatinine clearance (Cl_{Cr}) as 100 mL/min. Your therapeutic goal is an average [digoxin] ~ 1.0 µg/L. Using the above formulae, we can estimate the patient's Vd ~ 614 L and Cl ~ 9.84 L/hour for digoxin. What sort of maintenance dose do we require to maintain an average [digoxin] ~ 1.0 µg/L?

As we have done before, we utilize the equation for relating the rate of infusion and Cl to the steady state drug level, $rate_{in}$ = $[digoxin]_{SS}$ * Cl = 1.0 µg/L * 9.84 L/hour = 9.84 1.0 µg/hour. In a 24-hour day, the patient requires a maintenance dose of approximately 240 mg. But, how should this be divided? Once, twice or three times per day?

We need to calculate the elimination half-life, t1/2 = 0.693 * Vd / Cl = 0.693 * 614 L / 9.84 L/hour = 43 hours. Therefore, even if we dose digoxin once per day, this is still less than the expected elimination half-life and there should be minimal differences between peak and trough levels.

Try putting all of the above into the pharmacokinetic model. For the moment we are going to ignore distribution phase, so set ViF = 0.99. You should observe that it takes a long time to reach steady state, over one week. Obviously, we are going to require a loading dose. However, once steady state is reached, the patient's [digoxin] should be varying between 0.8 – 1.2 μg/L, which is what we want. Calculate an appropriate loading dose to bring the patient to 1.0 μg/L.

Loading dose = [digoxin] * Vd = 1.0 μg/L * 614 L = 614 μg. Try adding that to the model.

Now, let's see the consequences of digoxin's distribution phase. When digoxin is administered it first distributes in an initial (central) volume that is ~ 10% the final (central + peripheral) volume of distribution. Digoxin subsequently equilibrates with the peripheral volume with an apparent half-life ~ 30 minutes. Hence, we should set ViF = 0.1 and t1/2d = 0.5. Try it.

The effect should be dramatic. Immediately after IV injection, the patient's digoxin level soars to ~ 4 μg/L. This is a dangerously toxic drug concentration. However, the patient does NOT experience any toxicity. This is because the sites of action for digoxin reside in the peripheral volume NOT in the central volume. However, we are measuring drug levels from the central volume (i.e. the blood). The peripheral volume never experiences the dramatic peaks in drug level. After 3 – 5 distribution half-lives, the central and peripheral drug concentrations have equilibrated and blood drug levels are representative of the effective concentration at drug active sites. In general, on should avoid drawing a blood sample for digoxin quantitation too soon after administration (< 2 hours for IV injection).

Model 6: Case Example (Intermittent PO digoxin administration)

For demonstration of our final pharmacokinetic model, intermittent dosing with both absorption and distribution phases, we will continue with digoxin but now consider the effect of absorption with PO dosing. Digoxin is available in a number of oral formulations. We will consider tablets that are absorbed with an approximately one hour half-life and are 70% bioavailable. The closest dosage to our current 240 mg is a 250 mg tab. Hence, you need to set everything the same as our Model 5 example but change dose to 250, F to 0.7, and set t12a = 1.

The overall effect of delayed absorption is predictable: peaks are lower and later, troughs are a bit higher. We also note that 4 – 6 hours are required before the central and peripheral volumes equilibrate and blood levels are representative of the effective drug concentration at tissue active sites.