Summary of Pharmacokinetic Calculations

The following list was extracted from pharmacology lecture notes provided by Dr. Steven Shafer. It summarizes and embellishes the pharmacokinetic concepts presented:

1. The rate of change (decrease) when drug is injected into a 1 compartment model is

   $$\frac{dX}{dt} = -kX$$ (first order process)

2. The concentration following that injection is

   $C(t) = C_0 e^{-kt}$ where C_0 is the initial concentration

3. The half-life, t½ (time required for a 50% decrease), is

   $$t_{1/2} = \frac{0.693}{k}$$

4. If you know the time required for a 50% decrease, the rate constant, k, is

   $$k = \frac{0.693}{t_{1/2}}$$

5. The definition of concentration is

   $C = \frac{X}{V}$, where X is amount and V is volume

6. The concentration at time t following a bolus injection will be

   $C(t) = \frac{X_0}{V} e^{-kt}$ where $\frac{X_0}{V}$ is the initial concentration

7. If Cl_T is the total clearance (or flow) from a 1 compartment model, the rate at which drug leaves can be calculated

   $$\frac{dX}{dt} = C(Cl_T)$$

8. Since item 1 and item 7 are the same rate, it follows (after substituting X/V for C) that

$$\mathbf{k = \frac{Cl_T}{V}}$$

Substituting in equation 3, we get this important relationship

$$\mathbf{t_{1/2} = \frac{0.693(V)}{Cl_T}}$$

So, as clearance (Cl_T) increases, k increases, and the half-life decreases. As volume (V) increases, k decreases, and half-life increases.

9. During an infusion at rate k_0, the concentrations are described by the equation

   $\mathbf{C(t) = C_{ss}(1 - e^{-kt})}$ where C_{ss} is the concentration at steady-state.

10. The steady-state concentration can be calculated from infusion rate and clearance

    $$\mathbf{C_{ss} = \frac{k_0}{Cl_T}}$$

11. Half-lives describe the time for a 50% decrease in concentration following a bolus, and they also describe the time required to reach 50% of the steady-state concentration during an infusion. Following a bolus, the concentrations will be at 25%, 13%, 6%, and 3% of the initial concentration following 2, 3, 4, and 5 half-lives, respectively. During a constant-rate infusion, the concentration will reach 75%, 88%, 94%, and 97% of the steady-state concentration in 2, 3, 4, and 5 half-lives, respectively.

What do you do with this? Well:

1. If you know the amount of drug injected (X_0), and the concentration at time 0 (C_0), you can calculate the volume

   $$\mathbf{V = \frac{X_0}{C_0}}$$

2. If you know X_0, V, and k, then you can calculate the concentration at any given time t

   $$\mathbf{C(t) = \frac{X_0}{V} e^{-kt}}$$

3. If you know two concentrations, C_1 and C_2, obtained at times t_1 and t_2, respectively, you can calculate k as

$$\mathbf{k} = \frac{\mathbf{\ln(C_1) - \ln(C_2)}}{\mathbf{t_2 - t_1}}$$

4. If you want to know the clearance (the flow out of the compartment), you can calculate it as k(V). If k and V are not known, or if there are several values of k (multicompartment kinetics), you can still calculate

$$\mathbf{Cl_T} = \frac{\mathbf{dose}}{\mathbf{AUC}}$$ where AUC is the area under the time vs. concentration curve

5. If you know the initial target concentration you want to achieve, C_{target}, then you can calculate $X_{loading}$, the intravenous dose required to produce that concentration

$$\mathbf{X_{loading}} = \mathbf{C_{target}(V)}$$

6. If you want to maintain concentration C_{target}, then you must continuously infuse drug at the same rate it is leaving. Assuming that you first gave a bolus of C_{target} (V), the rate at which drug will leave will be C_{target} (Cl_T). Therefore your maintenance infusion $X_{maintenance}$ will be

$$\mathbf{X_{maintenance}} = \mathbf{C_{target}(Cl_T)}$$

Another exercise from Dr. Shafer:

Dr. Rosow was quite concerned that I wouldn't explain the basic concepts adequately. He specifically requested that I make sure that if you are going to give a medication to "Joe" (must be a friend of his), you can figure out the dose for Joe. I don't know Joe, but I do know a few things about a new drug that Carl has started Joe on: cephprololopam, an antibiotic that has beta blocking and anxiolytic properties:

- The clearance of cephprololopam is 0.2 liters/min
- The volume of distribution of cephprololopam is 20 liters
- The therapeutic concentration is 2 μg/ml.

1. Carl forgot to tell me the half-life of cephprololopam. What is it?
   Answer:

$$k = \frac{Cl_T}{V} = \frac{\left(0.2\frac{liters}{min}\right)}{20liters} = 0.01min^{-1}$$

$$t_{1/2} = \frac{0.693}{k} = 69min$$

2. What is Joe's initial dose of cephprololopam?
   Answer:

$$X_{loading} = C_{target}(V) = \left(2\frac{\mu g}{ml}\right)20liters = 40mg$$

3. How much drug should I give Joe to maintain a cephprololopam concentration of 2 μg/ml?
   Answer:

$$X_{maintenance} = C_{target}(Cl_T) = \left(2\frac{\mu g}{ml}\right)\left(\frac{0.2liters}{min}\right) = 0.4\frac{mg}{min}$$

4. I want to put Joe on an oral form of cephprololopam, which he will take every 24 hr. How much should I give Joe, assuming the the drug is completely absorbed, and I want Joe's concentrations, on average, to be at the target?
   Answer: Joe will need the same total amount of drug every 24 hr

$$\left(0.4\frac{mg}{min}\right)1440min = 576\frac{mg}{day}$$

5. How long will it take Joe to reach steady-state dosing with these repeated oral doses? Answer: 4-5 half-lives = 276-345 min, i.e., Joe will be at steady state dosing within the time course of the first dose!