PHARMACOKINETICS

Introduction

Pharmacokinetics is what the body does to the drug. As a summary, it encompasses administration, distribution, metabolism and excretion of the drug.

In this simulation, the graph area plots plasma concentration (mg/L) against time (h). The model behind the simulation uses a one-compartment approach for simplification. The one-compartment model assumes that the drug absorbed distributes rapidly and evenly throughout the body. Later in the practical, you may experiment with two-compartment model in the 'Advanced' simulation and compare the concentration-time graphs between the models.

Getting Started

Before we begin, here are some tips for operating the application.

1) If the application appears glitchy, please close the window and try again.
2) Clicking on the graph area will give you the coordinates of the point that you have just clicked in the bottom right panel "Coordinates Log". The log stores up to 5 sets of coordinates. Use this if you need measurements to find out the half-life, Tmax, or Cmax of the graph.
3) There is an Area Under Curve (AUC) calculator below the "Coordinates Log". It can integrate the area under curve within the time limits that you have entered. The AUC is proportional to the cumulative exposure to the drug.
4) Before you start the simulation, you may input a therapeutic range on the left-hand panel. The lower limit of the range, the blue line, indicates the therapeutic level. The upper limit of the range, the red line, indicates the toxic level of the drug. The red and blue lines are reference lines for you to see whether your drug is within the therapeutic range.
5) If the graph exceeds the range of the graph area or becomes too small to visualise clearly, please utilise the slider along the right of the graph to rescale the graph.
6) When working through the scenarios, using the 'Advanced' mode available at the bottom right corner of the application will allow you to enter custom values into the simulation.

Dosing Modes

1) Manual Dosing – A dose (oral/IV) is only given when the user presses G. This mode is useful for examining the change of plasma concentration over time after a single IV or oral dose. Note that manual dosing cannot be toggled on if either of "IV infusion" or "loading dose" is also toggled on (i.e. mutually exclusive). When manual dosing is toggled on, the parameter "Dosing Frequency" is not taken into account.
2) Repeated Dosing – A dose (oral/IV) is given after a set time interval as determined by the parameter "Dosing Frequency".
3) IV infusion – Continuous IV infusion at user specified rate. Concentration at steady state equals infusion rate divided by total clearance rate.
4) Loading Dose – Can be toggled on in conjunction with repeated dosing or IV infusion. Loading dose sets the quantity of the very first dose given at the start of the simulation.

5) Oral Dosing – If oral administration is selected (default is IV administration), you may change the following additional parameters in the oral control box.
    - Fraction of drug absorbed in GI
    - Hepatic extraction ratio – First pass metabolism of the drug
    - Absorption constant (Ka) – Rate of absorption of drug in GI.

Keeping in mind these dosing modes, here are some dosing scenarios that you can work through over the course of the practical.

1) Single IV Bolus
2) Single Oral Dose
3) Repeated IV Bolus +/- loading dose
4) Repeated Oral Dose +/- loading dose
5) IV Infusion +/- loading dose

<u>Information on the Pharmacokinetic Parameters</u>

1) Dosing Frequency
   You may have found that giving small doses with short dosing intervals leads to more stable control over plasma levels of the drug. However, keep in mind that short dosing intervals may be unfeasible for long-term medications. Taking a drug multiple times per day can cause inconvenience and therefore affect adherence to the treatment regimen.

2) Dose
   The dose range available range from 10 mg to 100 mg, in increments of 10 mg. As you increase the dose, note the changes in plasma levels of drug over time. Describe the rates of elimination over time. Also take note of the time taken for the dose to fall by half – the half-life of the drug.

3) Volume of Distribution
   As (apparent) volume of distribution can be a challenging concept for students new to pharmacokinetics, please refer to lecture slides or approach your demonstrator to clarify any questions that you may have.
   Changing the volume of distribution affects two important aspects of the concentration-time curve. What are these two aspects? (Answer: Peak plasma concentration and half-life)
   Use the simulator to see if you are right!
   Question: In repeated dosing, how does doubling the volume of distribution affect the dose of the drug?

4) Renal and Hepatic Clearance
   In renal failure, acute or chronic, drugs that rely mainly on renal clearance will start accumulating and reach toxic levels – you can simulate this by keeping all other parameters constant but reducing the renal clearance parameter.
   Hepatic clearance relies mainly on Cytochrome P450 enzymes (CYP). When these enzymes are inhibited by other drugs that the patient is taking, hepatic clearance decreases. Expression of these enzymes can be increased by some drugs as well, resulting in increased hepatic clearance!
   Question: How does clearance affect the AUC and half-life of the drug?

Practice: Calculate the half-life of a drug given the total clearance and volume of distribution. Check your answer against the simulation.
*** Half Life = ln(2) x (Volume of Distribution / Clearance).

Oral administration kinetics

Oral administration is more complicated than IV administration. However, IV administration requires IV access, which is painful and also comes with its own set of complications, such as IV line infections etc.

Oral administration is more convenient, much less painful, and more likely to encourage better adherence. But for oral administration, we need to consider a few additional factors. First, not all of the drug may be absorbed from the GI tract. This value can range from 0 to 1. 0 for drugs that are not absorbed from the GI at all, and 1 for drugs that are completely absorbed from the GI.

After absorption from the GI, the hepatic portal vein brings the absorbed drug to the liver, where the liver enzymes metabolise the drug straight away. You may know that this is called “First Pass Metabolism”. The hepatic extraction ratio quantifies what fraction of the drug is eliminated via hepatic metabolism. This value can also range from 0 to 1. 0 for drugs that are not metabolised in the liver at all, and 1 for drugs that are completely metabolised in the liver during first pass.

The absorption constant quantifies the rate of absorption of the drug from the GI. As drugs are subject to metabolism and clearance as soon as they are absorbed, changing the absorption constant will result in changes in the Cmax and Tmax. Cmax, and Tmax, will occur when the rate of absorption of the drug equals the rate of elimination of the drug.

Disclaimer: This simulation is for learning purposes only, clinical use not intended.