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TUTORIAL

Absorption and Half-Life

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This tutorial deals with basic concepts of absorption processes and links previous tutorials on clearance and volume of distribution to introduce the concept of half-life. The time course of both absorption and elimination are commonly described using a half-life. Half-life can also be used to describe drug accumulation. Understanding the principles underlying the time course of absorption and elimination are essential in pharmacotherapy and clinical pharmacology.

Principles of Absorption

Drug absorption can be described by two quite distinct factors.

The extent of absorption reflects the total amount of drug entering the body. It is not time dependent.

The rate of absorption determines how quickly the drug enters the body. The rate typically changes with time.

Extent of Absorption

The extent of oral absorption can be considered in 2 parts. The first part is the fraction of drug absorbed across the gut wall (f). This describes how much drug gets from the gut into the portal venous system. It is determined in part by physicochemical properties. Small, unionized molecules e.g. theophylline, are almost completely absorbed across the gut wall. Large, ionized molecules like gentamicin cross membranes with difficulty and only a small fraction is absorbed across the gut wall. Many drugs can cross the luminal cell membrane but are then metabolized in the gut wall (typically by CYP3A4 e.g. simvastatin) and/or transported out of the cell back into the gut lumen (typically by P-glyco-protein e.g. digoxin).

Hepatic blood flow is one of the determinants of hepatic clearance. If the intrinsic clearance of the liver (i.e. the metabolizing enzyme capacity) is high then almost all the drug entering the liver may be metabolized as it passes through the liver. This means most of the drug entering the liver is extracted. This is called first pass extraction. Hepatic extraction ratio (ER) is the fraction of drug entering the liver that is extracted. Morphine has a high intrinsic hepatic clearance and about 60% of morphine is removed by first pass extraction after an oral dose.

The hepatic extraction is determined both by the blood flow and by the intrinsic clearance. If blood flow is low then this gives the liver plenty of time to extract drug and extraction ratio will be high. On the other hand if the blood flow is high then drug can rush through the liver without being given a chance to be metabolized. If clearance is low then less drug is metabolized per unit time and extraction will be low. If clearance is high then more drug is metabolized per unit time and extraction will be high.

The extraction of ethanol by the liver is sensitive to the rate of delivery to the liver which is largely determined by the rate of absorption. If ethanol absorption is slowed down e.g. by food, then hepatic extraction is more effective and less ethanol reaches the systemic circulation.

The overall extent of absorption is called the bioavailability. It can be calculated from the product of the fraction absorbed across the gut (f) and the hepatic extraction ratio (ER). For morphine if we assume f of 1 and ER of 0.6 then oral bioavailability will be 40%. It is the fraction of the administered dose that reaches the systemic circulation.

Rate of Absorption

The rate of drug absorption can be described by one of 3 types of process.

1. Bolus input means absorption is instantaneous. It is approxi mated by rapid intra-venous injection.
2. Zero-order input means the absorption rate is constant for some defined period of time. This can be achieved by a con stant rate intra-venous infusion. It can also be approximated by some kinds of oral dosing.
3. First-order input means the absorption rate is proportional to the amount (or concentration) of drug at the absorption site. Typically this means that the absorption rate is higher immediately after the dose is given and the rate then decreases as drug is absorbed. Intra-muscular injection of drugs provides an example of a first-order input process.

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Constant Rate Input (Zero-order)

The stomach is not an organ of absorption. Very little drug is absorbed across the stomach wall. Drugs (and almost anything else) are absorbed primarily in the small intestine. When drugs dissolve rapidly in the stomach the rate of emptying of the stomach determines the delivery rate of drug to the duodenum. Absorption from the duodenum is usually rapid and the rate limiting factor is the rate of gastric emptying. As a rough approximation the rate of gastric emptying occurs at a constant rate. It is like a constant rate infusion from the stomach to the duodenum. Many drugs are absorbed at the same rate because it is gastric emptying not the drug that determines how quickly the drug gets into the blood.

Some drug formulations are specifically designed not to dissolve quickly. This means the drug formulation, not physiology, can be the rate limiting factor for absorption. Slow release (also known as controlled release or modified release) formulations can often appear to make input similar to a zero-order input process. For zero-order processes the key parameter is the duration of the process (Tk0).

$$C(t) = \frac{Rate}{CL} \bullet \left(1 - e^{-\frac{CL}{V} \cdot t}\right) \qquad \text{Equation 1}$$

Equation 1 predicts the time course of drug concentration in the blood from a constant rate input before the input process ends.

Figure 1 shows the time course of drug concentration and associated rates of elimination and input for a constant rate input over 1 hour. Note that the peak concentration occurs at the end of the constant rate input.

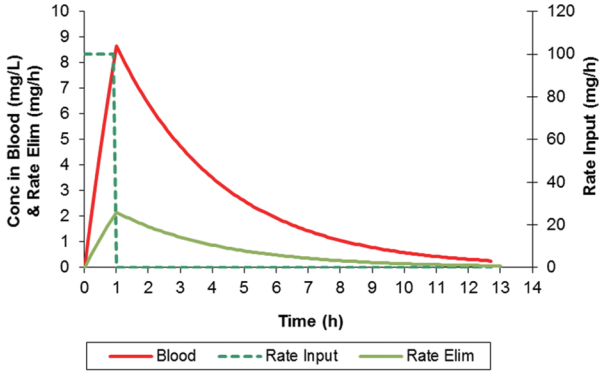

Figure 1

First-order Input

Absorption rate across the gut wall can be described by a first order process. The proportionality constant relating drug amount at the site of absorption to the rate of absorption is often called KA. This is a first order rate constant and is exactly related to the corresponding half-life for the absorption process. The absorption half- life can be calculated from KA using the natural log of 2 (i.e., absorption half-life 0.7/KA).

$$C(t) = \frac{Dose \bullet Ka}{V \bullet \left(Ka - \frac{CL}{V}\right)} \bullet \left(e^{-\frac{CL}{V} \cdot t} - e^{-Ka \cdot t}\right) \qquad \text{Equation 2}$$

Equation 2 predicts the time course of drug concentration in the blood from a first-order input process. The time of the peak concentration occurs when the rate of absorption is equal to the rate of elimination. Absorption is more than 90% complete after 4 absorption half-lives. The absorption half-life should not be confused with the elimination half-life. Typical absorption half-lives are less than 0.5 hour while elimination half-lives are often several hours or days.

Figure 2 shows the time course of drug concentration and associates rates of elimination and input for a first-order input. Note that the peak concentration occurs when the absorption rate is equal to the elimination rate at around 1.5 hours.

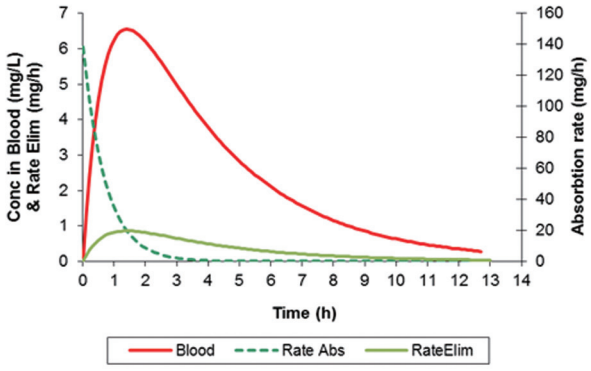

Figure 2

Clinical Applications of Principles of Absorption

The extent of absorption (bioavailability, F) is used to convert intravenous doses to an equivalent oral dose. An intravenous dose should be divided by F to get the equivalent oral dose e.g. digoxin has an oral bioavailability of about 67%. An intravenous dose of 500 micrograms would correspond to an oral dose of 750 micrograms.

The rate of drug absorption is a key determinant of the time of peak concentration and thus of the peak effect. Note that for drugs with an immediate effect, the peak effect is the effect at the time (Tmax) of the peak concentration (Cmax). The peak effect is not the same as the maximum possible effect of a drug (Emax).

Generic medicines are an important part of controlling drug

costs for healthcare. Generic drugs are typically much cheaper than the originator product. Regulatory authorities (e.g. MedSafe in NZ, FDA in USA) use the rate and extent of absorption to judge if a generic drug is bioequivalent to the originator product. Rate is usually judged on the basis of equivalent Cmax and Tmax while extent is judged on equivalent area under the concentration time curve (AUC).

Half-Life

Half-lives describe first-order processes. First-order processes are also often called exponential because an exponential function can be used to predict the time course of a first-order process.

Half-lives are commonly used in pharmacokinetics to describe drug absorption and elimination. The elimination half-life also determines how quickly a drug accumulates.

The elimination half-life is determined by clearance (CL) and the volume of distribution (V). A proportionality constant, ln(2), is needed to calculate the half-life. A useful approximation to ln(2) is 0.7.

The origin of using ln(2) as the proportionality constant can be shown by deriving the half-life from a differential equation for drug elimination.

$$\frac{dC}{dt} = -\frac{CL}{V} \bullet C$$

$$C(t) = C_0 \bullet e^{-\frac{CL}{V} \bullet t} \qquad 0.5 = 1 \bullet e^{-\frac{CL}{V} \bullet T_{½}}$$

$$\ln(0.5) = -\frac{CL}{V} \bullet T_{½} \qquad \ln(2) = \frac{CL}{V} \bullet T_{½}$$

$$T_{½} = \ln(2) \bullet \frac{V}{CL}$$

Time Course of Elimination and Accumulation

Table 1 and Figure 3 show how elimination and accumulation are mirror images of each other.

After one half-life a drug will be 50% eliminated. If a drug is administered by constant rate infusion (zero-order) it will accumulate to 50% of the steady state value after one half-life. If input continues then after 2 half-lives the concentration reaches 75% of steady state. Two half-lives after input stops then 75% of the drug will be eliminated. It is useful to learn the fraction of drug eliminated after 1, 2, 3 and 4 half-lives. After 4 half-lives elimination and accumulation can be considered essentially complete.

Figure 4 illustrates the time course of a drug (theophylline) given by constant rate infusion or by intravenous bolus dose every 8 h or every 16 h. The dose has been chosen so that the same total amount is given every 16 h. The average steady state concentration is the same for all 3 dosing regimens. Although the bolus dose regimens have swings between peak and trough they accumulate at exactly the same rate as the constant rate infusion.

All drugs accumulate. The extent of accumulation depends on the dosing interval and the half-life. A formula for predicting

Table 1.

Time	% Css	Concentration
0	0	100
1	50	50
2	75	25
3	87.5	12.5
4	93.8	6.25
5	96.9	3.1
6	98.4	1.6
7	99.2	0.8
8	99.6	0.4

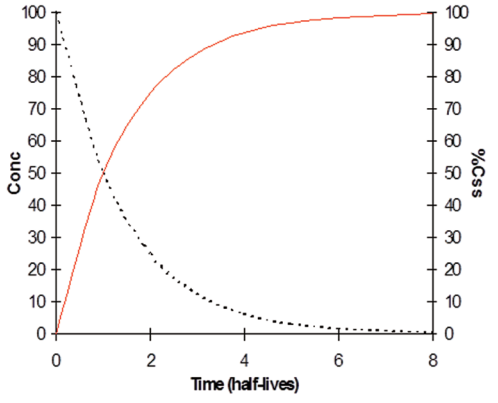

Figure 3

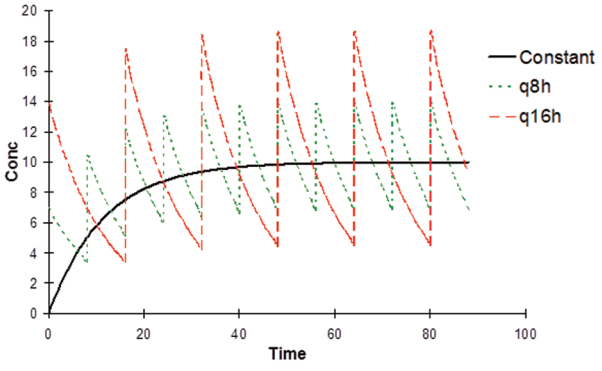

Figure 4

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$$AF = \frac{Conc(t)_{\text{ at Steady State}}}{Conc(t)_{\text{ after First Dose}}}$$

$$AF = \frac{1}{1 - e^{-CL/V \cdot \text{Dosint}}} \qquad \text{Equation 3}$$

accumulation is shown in Equation 3.

The accumulation factor (AF) is the ratio of the concentration at steady state to the concentration after the first dose at the same time after the dose. If the dosing interval is equal to the half-life then the accumulation factor is exactly 2.

For accumulation of a drug it is useful to predict that 50% accumulation is reached after one half-life and 75% after 2 half-lives. After 4 half-lives the drug accumulation will be close to steady state.

Clinical Applications of Half-Life

Drug accumulation is similar in time course to the time course of drug elimination. Essentially all drug is eliminated after 4 half-lives.

The absorption half-life can be used to predict the time (Tmax) of peak concentration for many drugs. Because the peak occurs when drug absorption is equal to drug elimination it happens before drug absorption is complete. An approximate way to predict Tmax is at 3 times the absorption half-life.

Conflict of Interest

The author has no conflict of interest.