

Basic pharmacokinetic concepts

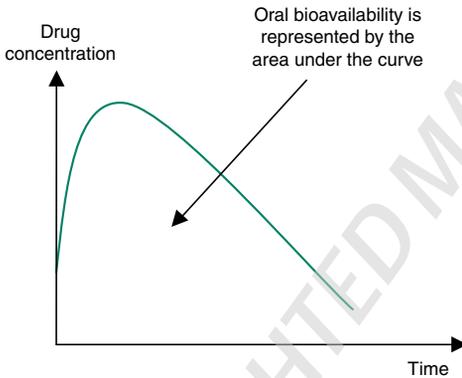
PHARMACOKINETICS The study of the movement of drugs into, within and out of the body. The key pharmacokinetic parameters from a dosing point of view are bioavailability (F), clearance (Cl), volume of distribution (V_d) and elimination half-life ($t_{1/2}$).

PHARMACODYNAMICS The study of the effect of a drug on the body.

BIOAVAILABILITY (F)

F is defined as the percentage of an administered dose that reaches the systemic circulation unchanged. Bioavailability is 100% for the intravenous route.

Oral bioavailability varies and is dependent on the degree of absorption, formulation of some drugs (e.g. nitrates) and the degree of first-pass hepatic metabolism. If plasma concentration is plotted against time, bioavailability is represented as the area under the curve.



VOLUME OF DISTRIBUTION (V_d)

V_d represents the theoretical volume into which a given drug dose must be distributed in the body to achieve a concentration equal to that of plasma. Drugs that are highly lipid soluble, such as digoxin, have a high V_d . Drugs that are lipid insoluble, such as neuromuscular blockers, remain predominantly in the plasma and will have a low V_d .

Clinically, the larger the volume of distribution the longer it will take to reach a therapeutic level and, therefore, a loading dose may be necessary. The volume of distribution can be calculated as:

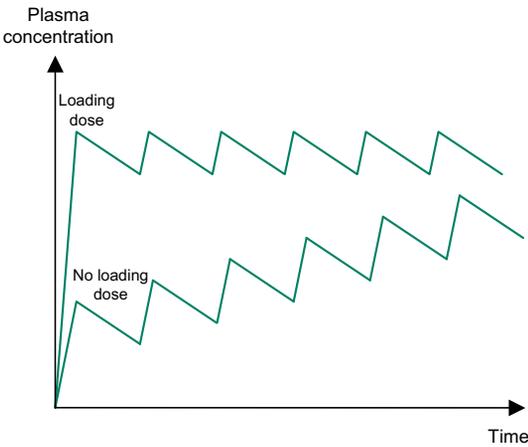
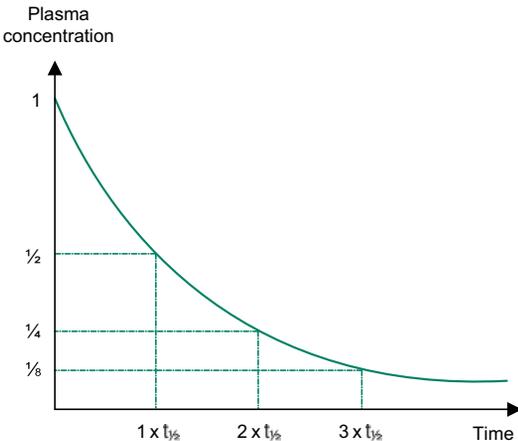
$$V_d = \frac{\text{Total amount of drug in body}}{\text{Plasma concentration of drug}}$$

LOADING DOSE

Defined as the initial dose of a drug required to rapidly achieve a desired plasma concentration. The time required to achieve a steady state plasma concentration will be long if a drug has a long $t_{1/2}$ (time taken to reach steady state is approximately $4\frac{1}{2}$ half-lives). Therefore it is desirable to administer a loading dose to attain a therapeutic plasma concentration immediately. Examples of drugs requiring a loading dose regime include amiodarone, digoxin and warfarin.

The main factor determining a loading dose is the volume of distribution (V_d). In order for a drug to reach a steady state plasma concentration (C_p), the tissues into which the drug distributes must be saturated first. The relationship between loading dose and volume of distribution is defined below:

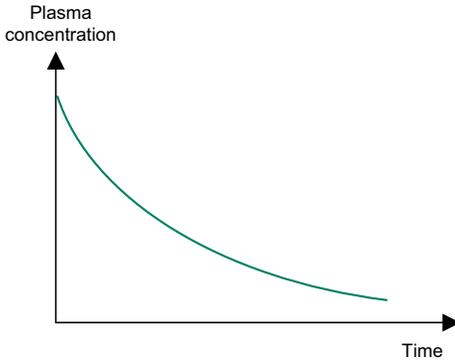
$$\text{Loading dose} = V_d \times C_p$$

**ELIMINATION HALF-LIFE ($t_{1/2}$)**

$t_{1/2}$ is the time taken for the plasma concentration of a drug to fall by 50%. The elimination rate constant (K) is the fraction of the total amount of drug in the body removed per unit time. K is represented by the slope of the line of the log plasma concentration versus time.

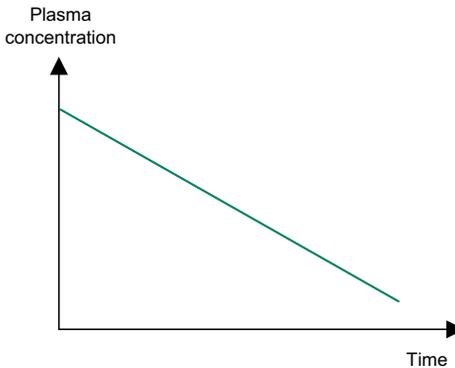
Elimination rate constant and $t_{1/2}$ can be used clinically to estimate the time to reach steady state concentrations after drug initiation or a change in maintenance dose.

FIRST-ORDER KINETICS



In first-order kinetics a constant fraction of the drug is eliminated per unit time. The rate of elimination is, therefore, proportional to the amount of drug in the body. The majority of drugs follow first-order kinetics.

ZERO-ORDER KINETICS



In zero-order kinetics the rate of drug elimination is linear and independent of drug concentration. Many important drugs, such as phenytoin and theophylline, follow zero-order kinetics at higher doses. Alcohol also follows zero-order kinetics with a decline in plasma levels at a constant rate of approximately 15 mg/100 ml/h.

CLEARANCE

Clearance is the theoretical volume of plasma from which the drug is completely removed per unit time. It is not the amount of drug removed from the body. Some of the factors that alter clearance include: degree of protein binding, body surface area, cardiac output, hepatic function and renal function.

Clearance can be calculated from the elimination rate constant and the volume of distribution:

$$Cl = K \times V_d$$