DRUG ELIMINATION

Drug elimination refers to the irreversible removal of drug from the body by all routes of elimination.
Drug elimination is usually divided into two major components: **excretion** and **biotransformation.**

Drug excretion is the removal of the intact drug.
Nonvolatile and polar drugs are excreted mainly by renal excretion. Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), or other body fluids. Volatile drugs, such as gaseous anesthetics, alcohol, or drugs with high volatility, are excreted via the lungs into expired air.

Biotransformation* or *drug metabolism is the process by which the drug is chemically converted in the body to a metabolite.

Drug elimination is described in terms of clearance from a hypothetical well-stirred compartment containing uniform drug distribution.

DRUG CLEARANCE

Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process.
There are several definitions for clearance, the simplest one is the fixed volume of fluid (containing the drug) removed from the drug per unit of time. The units for clearance are volume/ time (eg, mL/min, L/h). For example, if the *Cl* of penicillin is 15 mL/min in a patient and penicillin has a V_D of 12 L, then from the clearance definition, 15 mL of the 12 L will be removed from the drug per minute.

Clearance may also be defined as the rate of drug elimination divided by the plasma drug concentration.

$$\text{Cl} = \frac{Elemination\ rte}{Plasma\ concentration\ (Cp)}$$

$$\text{Cl} = \frac{dD_E/dt}{C_P} = \frac{\mu g/min}{\mu g/mL} = \text{mL/min}$$

Where D_E is the amount of drug eliminated and dD_E/dt is the rate of elimination.

Rearrangement of the above equation gives:

$$\text{Rate of elimination} = \frac{dD_E}{dt} = C_P\ Cl$$

The two definitions for clearance are similar because dividing the elimination rate by the C_P yields the volume of plasma cleared of drug per minute

For first-order elimination rate, dD_E/dt, equals kD_B *or* kC_PV_D therefore:

Cl = $\frac{kC_P V_D}{C_P}$ = k V_D

As both volume of distribution, V_D, and a rate constant, k, are constants when the PK is linear, clearance remains constant but the rate of drug elimination, dD_E/dt, might be different.

Example: Penicillin has a *Cl* of 15 mL/min. Calculate the elimination rate for penicillin when the plasma drug concentration, C_p, is 2 μg/mL.

Solution

Elimination rate = $C_p \times Cl$

dD_E/dt = 2 μg/mL x 15 mL/min = 30 μg/min.

Using the previous penicillin example, assume that the plasma penicillin concentration is 10 μg/mL.

dD_E/dt = 10 μg/mL x 15 mL/min = 150 μg/min

Thus, 150 μg/min of penicillin is eliminated from the body when the plasma penicillin concentration is 10 μg/mL.

Clearance may be used to estimate the rate of drug elimination at any given concentration. Using the same example, if the elimination rate of penicillin was measured as 150 μg/min when the plasma penicillin concentration was 10 μg/mL, then the clearance of penicillin is calculated:

Cl = $\frac{dD_E/dt}{C_P} = \frac{150\ \mu g/min}{10\ \mu g/mL}$ = 15 mL/min

- Elimination rate constant:

  $k = k_R + k_H + k_{other}$

Similarly, *Cl* is the total sum of all of the different clearance processes in the body

$Cl = Cl_R + Cl_H + Cl_{other}$

Renal clearance: $Cl_R = k_R \times V$

Hepatic clearance: $Cl_H = k_H \times V$

Total clearance:

$Cl = k \times V = (k_R + k_H + k_{other}) \times V$

Clearance calculations

Clearance can be calculated using compartmental, noncompartmental, or physiologic methods (all methods will lead to the same results if they are applied correctly).

- **Compartmental**

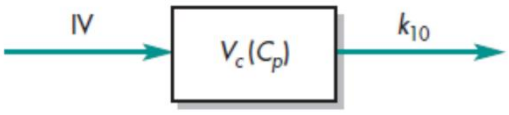
  One-compartment model

  $Cl = k \times V_D$

Multicompartment model

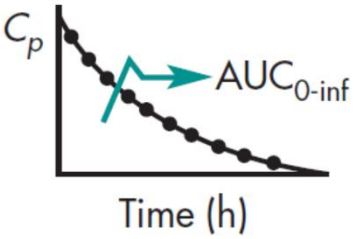
$Cl = k_{10} \times V_p = (k_R + k_H + k_{other}) \times V_p$

The volume of distribution used is the volume of the central compartment.



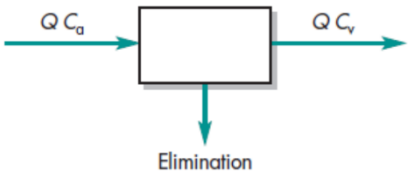
- **Non-compartmental**

Cl = DOSE/$AUC_{0\text{-inf}}$



- **Physiological model**

Clearance is the product of the flow through an organ (Q) and the extraction ratio of that organ (E). For example, the hepatic clearance is



$Cl_H = Q_H \times E_H$

Clearance values are often adjusted on a per-kilogram-of-actual-body-weight (ABW) or on a per-meter-square-of-surface-area basis, such as L/h per kilogram or per m^2, or normalized for a "typical" adult of 72 kg or 1.72 m2. This approach is similar to the method for expressing V, because both pharmacokinetic parameters vary with body weight or body size.

The Kidney

The kidney is the main excretory organ for the removal of metabolic waste products and plays a major role in maintaining the normal fluid volume and electrolyte composition in the body.

The ***renal blood flow*** **(RBF)** is the volume of blood flowing through the renal vasculature per unit of time. RBF exceeds 1.2 L/min or 1700 L/d. ***Renal plasma flow*** **(RPF)** is the RBF minus the volume of red blood cells present. RPF is an important factor in the rate of drug filtration at the glomerulus.

RPF = RBF - (RBF × Hct)

where Hct is the *hematocrit.*

Hct is the fraction of blood cells in the blood, about 0.45 or 45% of the total blood volume.

Rearrangement of the above equation gives

RPF = RBF (1 - Hct)

The average ***glomerular filtration rate*** **(GFR)** is about 120 mL/min in an average adult,[3] or about 20% of the RPF. The ratio **GFR/RPF** is the ***filtration fraction***.

Renal Drug Excretion

Renal excretion is a major route of elimination for many drugs. Drugs that are nonvolatile, are water soluble, have a low molecular weight (MW), or are slowly biotransformed by the liver are eliminated by renal excretion. The processes by which a drug is excreted via the kidneys may include any combination of the following:

1. Glomerular filtration
2. Active tubular secretion
3. Tubular reabsorption

Glomerular filtration

Glomerular filtration is a unidirectional process that occurs for most small molecules (MW < 500), including undissociated (nonionized) and dissociated (ionized) drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus.

Glomerular filtration rate (GFR) is measured by using a drug that is eliminated primarily by filtration only (ie, the drug is neither reabsorbed nor secreted). Clinically inulin and creatinine are used for this purpose, although creatinine is also secreted. **The clearance of inulin is approximately equal to the GFR, which can equal 120 mL/min.**

Active tubular secretion

Active tubular secretion is an active transport process. As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient. The carrier system is capacity limited and may be saturated. Drugs with similar structures may compete for the same carrier system.

Tubular reabsorption

Tubular reabsorption occurs after the drug is filtered through the glomerulus and can be an active or a passive process involving transporting back into the plasma. If a drug is completely reabsorbed (eg, glucose), then the value for the clearance of the drug is approximately zero. For drugs that are partially reabsorbed without being secreted, clearance values are less than the GFR of 120 mL/min.

The reabsorption of drugs that are acids or weak bases is influenced by the pH of the fluid in the renal tubule (ie, urine pH) and the pK_a of the drug.

The pKa of the drug is a constant, but the normal urinary pH may vary from 4.5 to 8.0, depending on diet, pathophysiology, and drug intake. Vegetable and fruit diets (alkaline residue diet) result in higher urinary pH, whereas diets rich in protein result in lower urinary pH.

Drugs such as ascorbic acid and antacids such as sodium carbonate may decrease (acidify) or increase (alkalinize) the urinary pH, respectively. Intravenous fluids, such as solutions of bicarbonate or ammonium chloride, are used in acid-base therapy to alkalinize or acidify the urine, respectively.

The ratio of ionisation is calculated according to ***Henderson and Hasselbalch* equation**

For weak acids, Ratio = $\frac{[\text{Salt}]}{[\text{Acid}]} = \frac{[\text{A}-]}{[\text{HA}]} = 10^{(\text{pH-p}K\text{a})}$

For weak bases, Ratio = $\frac{[\text{Base}]}{[\text{Salt}]} = \frac{[\text{B}]}{[\text{BH}+]} = 10^{(\text{pH-p}K\text{a})}$

For example, amphetamine, a weak base, will be reabsorbed if the urine pH is made alkaline and more lipid-soluble nonionized species are formed. In contrast, acidification of the urine will cause the amphetamine to become more ionized (form a salt). The salt form is more water soluble, less likely to be reabsorbed, and tends to be excreted into the urine more quickly. In the case of weak acids (such as salicylic acid), acidification of the urine causes greater reabsorption of the drug and alkalinization of the urine causes more rapid excretion of the drug.

From the Henderson-Hasselbalch relationship, a concentration ratio for the distribution of a weak acid or basic drug between urine and plasma may be derived. The urine-plasma (*U/P*) ratios for these drugs are as follows.

For weak acids,

$$\frac{U}{P} = \frac{1 + 10^{pH_{urine} - pK_a}}{1 + 10^{pH_{plasma} - pK_a}}$$

For weak bases,

$$\frac{U}{P} = \frac{1 + 10^{pK_a - pH_{urine}}}{1 + 10^{pK_a - pH_{plasma}}}$$

Practice problem

Let pKa = 5 for an acidic drug. Compare the *U*/*P* at urinary pH **(a)** 3, **(b)** 5, and **(c)** 7.

Solution

a. At pH = 3,

$$\frac{U}{P} = \frac{1 + 10^{3-5}}{1 + 10^{7.4-5}} = \frac{1}{252}$$

b. At pH = 5,

$$\frac{U}{P} = \frac{1 + 10^{5-5}}{1 + 10^{7.4-5}} = \frac{2}{252}$$

c. At pH = 7,

$$\frac{U}{P} = \frac{1 + 10^{7-5}}{1 + 10^{7.4-5}} = \frac{101}{252}$$

Renal clearance

Renal clearance, Cl_R, is defined as the volume that is removed from the drug per unit of time through the kidney. Also it can be defined as the urinary drug excretion rate (dD_u/dt) divided by the plasma drug concentration (C_p).

$$Cl = \frac{dD_U/dt}{C_P}$$

The total body clearance can be defined as the sum of the renal clearance (Cl_R) and the nonrenal clearance (Cl_{NR})

$$Cl = Cl_R + Cl_{NR}$$

Therefore, $Cl_R = f_e \times Cl$

where f_e is the proportion of the bioavailable dose that is eliminated unchanged in the urine.

Since $Cl = DOSE/AUC_{0\text{-inf}}$
Then renal clearance after sing IV administration is

$$Cl_R = \frac{f_e \text{ x Dose}}{AUC_{0-inf}}$$

$$Cl_R = \frac{Ae_{0-inf}}{AUC_{0-inf}}$$

where $Ae_{0\text{-inf}}$ is the amount of drug eliminated unchanged in the urine from time 0 to infinity after a single dose.

In practice it is not possible to measure the amount of drug excreted unchanged in the urine until infinity. Therefore, it is recommended to collect the urine and observe the AUC for the longest time period possible, ideally more than 3-4 terminal half-lives, so that the error made using this formula is less than 10%.

$$Cl_R = \frac{Ae_{0-x}}{AUC_{0-x}}$$

where x is the maximum length of time during which both urinary excreted amounts and the AUC can be observed.

Practice problem

An antibiotic is given by IV bolus injection at a dose of 500 mg. The drug follows a one-compartment model. The total volume of distribution was 21 L and the elimination half-life was 6 hours. Urine was collected for 48 hours, and 400 mg of unchanged drug was recovered. What is the fraction of the dose excreted unchanged in the urine? Calculate k, k_R, Cl, Cl_R, and Cl_{NR}.

Solution

Since the elimination half-life, $t_{1/2}$, for this drug is 6 hours, a urine collection for 48 hours represents $8 \times t_{1/2}$, which allows for greater than 99% of the drug to be eliminated from the body.
The fraction of drug excreted unchanged in the urine, fe, is calculated by the following equation: