**Drug Elimination and Clearance**

**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 mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately into the urine.

**Biotransformation or drug metabolism** is the process by which the drug is chemically converted in the body to a metabolite. Biotransformation is usually an enzymatic process. The enzymes involved in the biotransformation of drugs are located mainly in the liver.

Drug elimination is described in terms of clearance from a well-stirred compartment containing uniform drug distribution. The term clearance describes the process of drug elimination from the body or from a single organ without identifying the individual processes involved. Clearance may be defined as the volume of fluid cleared of drug from the body per unit of time. The units for clearance are milliliters per minute (mL/min) or liters per hour (L/hr). The volume concept is simple and convenient, because all drugs are dissolved and distributed in the fluids of the body.

The advantage of the clearance approach is that clearance applies to all elimination rate processes, regardless of the mechanism for elimination. In addition, for first-order elimination processes, clearance is a constant, whereas drug elimination rate is not constant.

**RENAL DRUG EXCRETION**

Renal excretion is a major route of elimination for many drugs. Drugs that are nonvolatile, 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:

- Glomerular filtration
- Active tubular secretion
- Tubular reabsorption

1. **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. The major driving force for glomerular filtration is the hydrostatic pressure within the glomerular capillaries. The kidneys receive a large blood supply (approximately 25% of the cardiac output) via the renal artery, with very little decrease in the hydrostatic pressure.

Glomerular filtration rate (GFR) is measured by using a drug that is eliminated by filtration only (ie, the drug is neither reabsorbed nor secreted). Examples of such drugs are inulin and creatinine. Therefore, the clearance of inulin is equal to the GFR, which is equal to 125-130 mL/min. The value for the GFR correlates fairly well with body surface area.

Glomerular filtration of drugs is directly related to the free or nonprotein-bound drug concentration in the plasma. As the free drug concentration in the plasma increases, the glomerular filtration for the drug increases proportionately, thus increasing renal drug clearance for some drugs.

2. **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. Two active renal secretion systems have been identified, systems for (1) weak acids and (2) weak bases. Probenecid competes with penicillin for the same carrier system (weak acids). Active tubular secretion rate is dependent on renal plasma flow. Drugs commonly used to measure active tubular secretion include p-amino-hippuric acid (PAH) and iodopyracet (Diodrast). These substances are both filtered by the glomeruli and
secreted by the tubular cells. The clearance for these drugs therefore reflects the effective renal plasma flow (ERPF), which varies from 425 to 650 mL/min. For a drug that is excreted solely by glomerular filtration, the elimination half-life may change markedly in accordance with the binding affinity of the drug for plasma proteins.

In contrast, drug protein binding has very little effect on the elimination half-life of the drug excreted mostly by active secretion. Because drug protein binding is reversible, drug bound to plasma protein rapidly dissociates as free drug is secreted by the kidneys. For example, some of the penicillins are extensively protein bound, but their elimination half-lives are short due to rapid elimination by active secretion.

3. **Tubular reabsorption** occurs after the drug is filtered through the glomerulus and can be an active or a passive process. 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, clearance values are less than the GFR of 125-130 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 pKa of the drug. Both of these factors together determine the percentage of dissociated (ionized) and undissociated (nonionized) drug.

The undissociated drug is easily reabsorbed from the renal tubule back into the body. The pKa of the drug is a constant, depending on diet, pathophysiology, and drug intake.

Intravenous fluids, such as solutions of bicarbonate or ammonium chloride, are used in acid-base therapy. Excretion of these solutions may drastically change urinary pH and alter drug reabsorption and drug excretion by the kidney.

The percentage of ionized weak acid drug corresponding to a given pH can be obtained from the *Henderson-Hasselbalch equation*.

\[
pH = pK_a + \log \left( \frac{\text{ionized}}{\text{nonionized}} \right) \quad \ldots \ldots 1
\]

Rearrangement of this equation yields

\[
\frac{\text{ionized}}{\text{nonionized}} = 10^{pH - pK_a}
\]
The extent of dissociation is more greatly affected by changes in urinary pH for drugs with a pKa of 5 than with a pKa of 3. Weak acids with pKa values of less than 2 are highly ionized at all urinary pH values and are only slightly affected by pH variations. The greatest effect of urinary pH on reabsorption occurs with weak base drugs with pKa values of 7.5-10.5.

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.

\[
\text{fraction of drug ionized} = \frac{\text{ionized}}{\text{ionized} + \text{nonionized}}
\]
\[
= \frac{10^{pH-pK_a} \text{(nonionized)}}{\text{ionized} + \text{nonionized}}
\]
\[
= \frac{10^{pH-pK_a}}{1 + 10^{pH-pK_a}}
\]

The extent of dissociation is more greatly affected by changes in urinary pH for drugs with a pKa of 5 than with a pKa of 3. Weak acids with pKa values of less than 2 are highly ionized at all urinary pH values and are only slightly affected by pH variations. The greatest effect of urinary pH on reabsorption occurs with weak base drugs with pKa values of 7.5-10.5.

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,
\[
\frac{U}{P} = \frac{1 + 10^{pH_{\text{urine}}-pK_a}}{1 + 10^{pH_{\text{plasma}}-pK_a}}
\]

For weak bases,
\[
\frac{U}{P} = \frac{1 + 10^{pK_a-pH_{\text{urine}}}}{1 + 10^{pK_a-pH_{\text{plasma}}}}
\]

amphetamine, a weak base, will be reabsorbed if the urine pH is made alkaline and more lipidsoluble 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 and less likely to be reabsorbed and has a tendency 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.
In summary, renal drug excretion is a composite of [1] passive filtration at the glomerulus (i.e.; the extent of reabsorption of weak acid or weak base drugs is influenced by the pH of the urine and the degree of ionization of the drug), [2] active secretion in the proximal tubule (i.e.; an enzyme (transporter)-mediated process that is saturable) and [3] passive reabsorption in the distal tubule. In addition, an increase in blood flow to the kidney, due to diuretic therapy or large alcohol consumption, decreases the extent of drug reabsorption in the kidney and increases the rate of drug excreted in the urine.

**DRUG CLEARANCE**

Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process. Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time. Alternatively, $ClT$ may be defined as the rate of drug elimination divided by the plasma drug concentration. This definition expresses drug elimination in terms of the volume of plasma eliminated of drug per unit time. This definition is a practical way to calculate clearance based on plasma drug concentration data.

\[
Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration}(C_p)} \quad \ldots\ldots5
\]

\[
Cl_T = \frac{dD_t/dt}{C_p} = \frac{\mu g/\text{min}}{\mu g/mL} = \text{mL/min} \quad \ldots\ldots6
\]

Where $D_E$ is the amount of drug eliminated and $dD_E/dt$ is the rate of elimination. Rearrangement of Equation 6 gives

\[
\text{Elimination rate} = \frac{dD_t}{dt} = C_pCl_T \quad \ldots\ldots7
\]

Based on Equation 5, substituting elimination rate for $kC_pV_p$, gives

\[Cl_T = \frac{kC_pV_D}{C_p} = kV_D \quad \ldots\ldots8\]
Equation 8 shows that clearance is the product of $V_D$ and $Cl_T$, both of which are constant. As the plasma drug concentration decreases during elimination, the rate of drug elimination, $E/\text{d}t$, decreases accordingly, but clearance remains constant. Clearance is constant as long as the rate of drug elimination is a first-order process.

**Example 1:**

Penicillin has a $Cl_T$ of 15 mL/min. Calculate the elimination rate for penicillin when the plasma drug concentration, $p$, is 2 µg/mL.

**Solution**

Elimination rate = $C_p \times Cl_T$

\[
\frac{dD_E}{dt} = 2 \text{ µg/mL} \times 15 \text{ mL/min} = 30 \text{ µg/min}
\]

Assume that the plasma penicillin concentration is 10 g/mL. The rate of drug elimination is

\[
\frac{dD_E}{dt} = 10 \text{ µg/mL} \times 15 \text{ mL/min} = 150 \text{ µg/min}
\]

If the elimination rate of penicillin was measured as 150 g/min when the plasma penicillin concentration was 10 g/mL, then the clearance of penicillin is

\[
Cl_{\text{penicillin}} = \frac{150 \text{ µg/min}}{10 \text{ µg/mL}} = 15 \text{ mL/min}
\]

Clearance values are often normalized on a per-kilogram body-weight basis, such as milliliters per minute kilogram. This approach is similar to the method for expressing $V_D$, because both pharmacokinetic parameters vary with body weight. The clearance for an individual patient is estimated as the product of the clearance per kilogram multiplied by the body weight (kg) of the patient.
Example 2:

Determine the total body clearance for a drug in a 70-kg male patient. The drug follows the kinetics of a one compartment model and has an elimination half-life of 3 hours with an apparent volume of distribution of 100 mL/kg.

Solution

First determine the elimination rate constant (k) and then substitute properly into Equation 8.

\[
k = \frac{0.693}{t_{1/2}} = \frac{0.693}{3} = 0.231 \text{ hr}^{-1}
\]

\[
C_{lt} = 0.231 \text{ hr}^{-1} \times 100 \text{ mL/kg} = 23.1 \text{ mL/kg hr}
\]

For a 70-kg patient,

\[
C_{lt} = 23.1 \text{ mL/kg} \times 70 \text{ kg} = 1617 \text{ mL/hr}
\]

CLEARANCE MODELS

The calculation of clearance from k and V D assumes (sometimes incorrectly) a defined model, whereas clearance estimated directly from the plasma drug concentration time curve does not assume any model. Although clearance may be regarded as the product of k and D, Equation 6.10 is far more general because the reaction order for the rate of drug elimination, dD/dt, is not specified, and the elimination rate may or may not follow first-order kinetics.

Physiologic/Organ Clearance

Physiologic pharmacokinetic models are based on drug clearance through individual organs or tissue groups (figure 1)
Figure 1: Drug clearance model. ($Q = \text{blood flow}$, $C_a = \text{incoming drug concentration [usually arterial drug concentration]}$, $C_v = \text{outgoing drug concentration [venous drug concentration]}$).

For any organ, clearance may be defined as the fraction of blood volume containing drug that flows through the organ and is eliminated of drug per unit time. From this definition, clearance is the product of the blood flow ($Q$) to the organ, and the extraction ratio (ER). The ER is the fraction of drug extracted by the organ as drug passes through.

\[
\text{Clearance} = Q(\text{ER})
\]  

…..9

If the drug concentration in the blood ($C_a$) entering the organ is greater than the drug concentration of blood ($C_v$) leaving the organ, then some of the drug has been extracted by the organ ($\text{ER}$). The ER is $C_a - C_v$ divided by the entering drug concentration ($C_a$), as shown in Equation 10.

\[
\text{ER} = \frac{C_a - C_v}{C_a}
\]  

…..10

ER is a ratio with no units. The value of ER may range from 0 (no drug removed by the organ) to 1 (100% of the drug is removed by the organ). Substituting for ER into Equation 9 yields

\[
Cl = Q\left(\frac{C_a - C_v}{C_a}\right)
\]  

……..11
Model-Independent Methods

Clearance is commonly used to describe first-order drug elimination from compartment models such as the one-compartment model, \( C(t) = C_p = C_p 0 e^{-kt} \) in which the distribution volume and elimination rate constant are well defined.

Clearance estimated directly from the plasma drug concentration-time curve does not assume any model. However, any elimination process other than a first-order rate process becomes complex and difficult to relate clearance to a compartment model.

*Model-independent methods* are non-compartment model approaches used to calculate certain pharmacokinetic parameters such as clearance and bioavailability (\( F \)). Clearance can be determined directly from the plasma-time concentration curve by

\[
Cl = \int_0^\infty \frac{D_0}{C(t)} \, dt
\]  

\[12\]

Where \( D_0 \) is the dose and \( C(t) \) is an unknown function that describes the declining plasma drug concentrations.

In the compartment model, \( C(t) = C_p = C_p 0 e^{-kt} \) can be different mathematical functions that describe the individual pharmacokinetics of the drug. Using the non-compartment approach, the general equation uses area under the curve of the plasma drug concentration curve, \([AUC]0^\infty\) for the calculation of clearance.

\[
Cl = \frac{D_0}{[AUC]0^\infty}
\]  

\[13\]

where \( D_0 \) is the dose and \([AUC]0^\infty = \int_0^\infty C_p \, dt\)
Because $[\text{AUC}]_0^{\infty}$ is calculated from the plasma drug concentration-time curve from 0 to infinity using the trapezoidal rule, no compartmental model is assumed.

However, to extrapolate the data to infinity to obtain the residual $[\text{AUC}]_t^{\infty}$ or $(C_p t/k)$, first-order elimination is usually assumed. This calculation of Cl T is referred to as a non-compartment or model-independent method. In this case, if the drug follows the kinetics of a one-compartment model, the Cl T is numerically similar to the product of $V_D$ and $k$ obtained by fitting the data to a one-compartment model.

**RENTAL CLEARANCE**

Renal clearance, $\text{Cl}_R$, is defined as the volume of plasma that is cleared of drug per unit of time through the kidney. Similarly, renal clearance may be defined as a constant fraction of the $V_D$ in which the drug is contained that is excreted by the kidney per unit of time. More simply, renal clearance is defined as the urinary drug excretion rate $(dD_u/dt)$ divided by the plasma drug concentration $(C_p)$.

\[
\text{Cl}_R = \frac{\text{excretion rate}}{\text{plasma concentration}} = \frac{dD_u/dt}{C_p}
\]

……..14

Rate of drug passing through kidney = rate of drug excreted

\[
\text{Cl}_R \times C_p = Q_u \times C_u
\]

mL/min $\times$ mg/mL = mL/min $\times$ mg/mL

……..15

Where $\text{Cl}_R$ is renal clearance, $C_p$ is plasma drug concentration, $Q_u$ is the rate of urine flow, and $C_u$ is the urine drug concentration. Rearrangement of Equation 15 gives:

\[
\text{Cl}_R = \frac{Q_u C_u}{C_p} = \frac{\text{excretion rate}}{C_p}
\]

……..16

Because the excretion rate $= Q_u C_u = dD_u/dt$, Equation 16 is the equivalent of Equation 14.
**Comparison of Drug Excretion Methods**

Renal clearance may be measured without regard to the physiologic mechanisms involved in this process. From a physiologic viewpoint, however, renal clearance may be considered as the ratio of the sum of the glomerular filtration and active secretion rates less the reabsorption rate divided by the plasma drug concentration:

\[
Cl_R = \frac{\text{filtration rate + secretion rate} - \text{reabsorption rate}}{C_p}
\]

The actual renal clearance of a drug is not generally obtained by direct measurement. The clearance value for the drug is often compared to that of a standard reference, such as inulin, which is cleared completely through the kidney by glomerular filtration only. The clearance ratio, which is the ratio of drug clearance to inulin clearance, may give an indication for the mechanism of renal excretion of the drug.

**Table 2: Comparison of Clearance of a Sample Drug to Clearance of a Reference Drug, Inulin**

<table>
<thead>
<tr>
<th>Clearance ratio</th>
<th>Probable mechanism of renal excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{CL_{drug}}{CL_{inulin}} &lt; 1 )</td>
<td>Drug is partially reabsorbed</td>
</tr>
<tr>
<td>( \frac{CL_{drug}}{CL_{inulin}} = 1 )</td>
<td>Drug is filtered only</td>
</tr>
<tr>
<td>( \frac{CL_{drug}}{CL_{inulin}} &gt; 1 )</td>
<td>Drug is actively secreted</td>
</tr>
</tbody>
</table>

**FILTRATION ONLY**

If glomerular filtration is the sole process for drug excretion and no drug is reabsorbed, then the amount of drug filtered at any time (t) will always be \( C_p \times GFR \)
<table>
<thead>
<tr>
<th>Time (min)</th>
<th>C(p) (g/ml)</th>
<th>Excretion Rate (g/min) (Drug Filtered by GFR per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(C(p))_0</td>
<td>(C(p))_0 \times 125</td>
</tr>
<tr>
<td>1</td>
<td>(C(p))_1</td>
<td>(C(p))_1 \times 125</td>
</tr>
<tr>
<td>2</td>
<td>(C(p))_2</td>
<td>(C(p))_2 \times 125</td>
</tr>
<tr>
<td>t</td>
<td>(C(p))_t</td>
<td>(C(p))_t \times 125</td>
</tr>
</tbody>
</table>

Likewise, if the Cl\(R\) of the drug is by glomerular filtration only, as in the case of inulin, then Cl\(R\) = GFR. Otherwise, Cl\(R\) represents all the processes by which the drug is cleared through the kidney, including any combination of filtration, reabsorption, and active secretion.

The rate of drug excretion using a compartment approach and physiologic approach are

\[
\frac{dD_b}{dt} = k_e V_D C_p \text{ (compartment)}
\]

......18

\[
\frac{dD_b}{dt} = Cl_R C_p \text{ (physiologic)}
\]

......19

Equating 18 and 19

\[k_e V_D C_p = Cl_R C_p\]

\[k_e = \frac{Cl_R}{V_D}\]......20

Equation 20 shows that, in the absence of other processes of drug elimination, the excretion rate constant are a fractional constant reflecting the volume pumped out per unit time due to GFR relative to the volume of the body compartment (V\(_D\)).

**FILTRATION AND REABSORPTION**

For a drug with a reabsorption fraction of fr, the drug excretion rate is reduced, and Equation 19 is restated as Equation 21:
Equating the right sides of Equations 21 and 18 indicates that the first-order rate constant \( (k_e) \) in the compartment model is equivalent to \( \text{Cl}_R (1 - fr) / V_D \). In this case, the excretion rate constant is affected by the reabsorption fraction \( (fr) \) and the GFR. Because these two parameters generally remain constant, the general adoption of a first-order elimination process to describe renal drug excretion is a reasonable approach.

**FILTRATION AND ACTIVE SECRETION**

For a drug that is primarily filtered and secreted, with negligible reabsorption, the overall excretion rate will exceed GFR. At low drug plasma concentrations, active secretion is not saturated, and the drug is excreted by filtration and active secretion. At high concentrations, the percentage of drug excreted by active secretion decreases due to saturation. Clearance decreases because excretion rate decreases (figure 3). Clearance decreases because the total excretion rate of the drug increases to the point where it is approximately equal to the filtration rate (figure 4).

**Figure 3: Excretion rate-versus-plasma level curves for a drug that demonstrates active tubular secretion and a drug that is secreted by glomerular filtration only.**

**Figure 4: Graph representing the decline of renal clearance.** As the drug plasma level increases to a concentration that saturates the active tubular secretion, glomerular filtration becomes the major component for renal clearance.
**Example 3**

Two drugs, A and B, are entirely eliminated through the kidney by glomerular filtration (125 mL/min), with no reabsorption. Drug A has half the distribution volume of drug B, and the $V_D$ of drug B is 20 L. What are the drug clearances for each drug based on the classical and physiologic approaches?

**Solution**

Since glomerular filtration of the two drugs is the same, and both drugs are not eliminated by other means, clearance for both drugs depends on renal plasma flow and extraction by the kidney only. Basing the clearance calculation on the physiologic definition and using Equation 11 results in

\[
Cl = \frac{Q(C_a - C_v)}{C_a} = 125 \text{ mL/min}.
\]

Basing the calculation on the elimination concept and applying Equation 6.14, $k$ is easily determined, resulting in an obvious difference in $t_{1/2}$ between the two drugs-in spite of similar drug clearance.

\[
k_{\text{drug A}} = \frac{Cl}{V_D} = \frac{125 \text{ mL/min}}{10\times1000 \text{ mL}} = 0.0125 \text{ min}^{-1}
\]

\[
k_{\text{drug B}} = \frac{Cl}{V_D} = \frac{125 \text{ mL/min}}{200 \times 1000 \text{ mL}} = 0.00625 \text{ min}^{-1}
\]

In spite of identical drug clearances, $k$ for drug A is twice that of drug B. Drug A has an elimination half-life of 80 minutes, while that of drug B is 160 minutes-much longer because of the bigger volume of distribution.

**DETERMINATION OF RENAL CLEARANCE**

**Graphical Methods** The clearance is given by the slope of the curve obtained by plotting the rate of drug excretion in urine ($dD_u/dt$) against $C_p$ (Eq. 22)

\[
Cl_R = \frac{dD_u/dt}{C_p} \quad \ldots22
\]
By rearranging Equation 22 and integrating:

\[
\int_{0}^{D_u} dD_u = Cl_R \int_{0}^{t} C_p \, dt \\
[D_u]_0 = Cl_R [AUC]_0
\]

\[\ldots\ldots\ldots23\]

A graph is then plotted of cumulative drug excreted in the urine versus the area under the concentration-time curve (figure 6). Renal clearance is obtained from the slope of the curve.

*Figure 6: Cumulative drug excretion versus AUC. The slope is equal to Cl R.*

By plotting cumulative drug excreted in the urine from t_1 to t_2, \([D_u]_{t_1}^{t_2}\) versus \([AUC]_{t_1}^{t_2}\), one obtains an equation similar to that presented previously:

\[
\int_{D_u}^{D_u} dD_u = Cl_R \int_{t_1}^{t_2} C_p \, dt \\
[D_u]_{t_1}^{t_2} = Cl_R [AUC]_{t_1}^{t_2}
\]

\[\ldots\ldots\ldots24\]

The slope is equal to the renal clearance (figure 7).
Model-Independent Methods

Clearance rates may also be estimated by a single (nongraphical) calculation from knowledge of the $[AUC]_0\infty$, the total amount of drug absorbed, $FD_0$, and the total amount of drug excreted in the urine, $D_{u\infty}$. For example, if a single IV bolus drug injection is given to a patient and the $[AUC]_0\infty$ is obtained from the plasma drug level-time curve, then total body clearance is estimated by:

$$Cl_T = \frac{D_0}{[AUC]_0\infty}$$

......25

If the total amount of drug excreted in the urine, $D_{u\infty}$ has been obtained, and then renal clearance is calculated by:

$$Cl_R = \frac{D_{u\infty}}{[AUC]_0\infty}$$

......26

RELATIONSHIP OF CLEARANCE TO ELIMINATION HALF-LIFE AND VOLUME OF DISTRIBUTION

The half-life of a drug can be determined if the clearance and $V_D$ are known.

$$Cl_T = kV_D$$

$$k = \frac{0.693}{t_{1/2}}$$
Therefore, by substitution,

\[ Cl_T = \frac{0.693 \cdot V_D}{t_{1/2}} \]

…..27

From Equation 27, as \( Cl_T \) decreases, which might happen in the case of renal insufficiency, the \( t_{1/2} \) for the drug increases?

**Total Body Clearance of Drugs after Intravenous Infusion:**

When drugs are administered by intravenous infusion, the total body clearance is obtained with the following equation:

\[ Cl_T = \frac{R}{C_{SS}} \]

…..28

where \( C_{SS} \) is the steady-state plasma drug concentration and \( R \) is the rate of infusion. Equation 28 is valid for drugs that follow either the one- or the two-compartment open model.

**Example 4:** A new antibiotic is actively secreted by the kidney; \( V_D \) is 35 L in the normal adult. The clearance of this drug is 650 mL/min.

1. What is the usual \( t_{1/2} \) for this drug?

\[ t_{1/2} = \frac{0.693 \cdot (35,000 \text{ mL})}{650 \text{ mL/min}} \]

\[ t_{1/2} = 37.3 \text{ min} \]

2. What would be the new \( t_{1/2} \) for this drug in an adult with partial renal failure whose clearance of the antibiotic was only 75 mL/min?

\[ t_{1/2} = \frac{0.693 \cdot (35,000 \text{ mL})}{75 \text{ mL/min}} \]

\[ t_{1/2} = 323 \text{ min} \]
FREQUENTLY ASKED QUESTIONS

1. Is clearance a better parameter to describe drug elimination than half-life? Why is it necessary to use both parameters in the literature?

**Answer:** Elimination half-life, \( t_{1/2} \), is a concise and informative term that describes the time needed for half the dose to be removed from the body. Alternatively, the elimination half-life indicates the time for the plasma drug concentration to decline to one-half from whatever concentration it started at. Classical pharmacokinetic models are based on \( t_{1/2} \) (or \( k \)) and \( V_D \). Some pharmacokineticists prefer \( Cl \) and \( V_D \), and regard \( t_{1/2} \) as a derived parameter.

2. What is an independent parameter in a model? Is clearance an independent parameter of the physiologic model? How is clearance related to parameters in the compartment model?

**Answer:** A parameter is a model-based numerical constant estimated statistically from the data. Model parameters are used generally to make predictions about the behavior of the real process. A parameter is termed independent if the parameter is not dependent on other parameters of the model. In the classical one-compartment model, \( k \) and \( V_D \) are independent model parameters, and \( t_{1/2} \) and \( Cl \) are regarded as derived parameters. In the physiologic model, \( Cl \) and \( V_D \) are regarded as independent model parameters, while \( k \) is a dependent parameter since \( k \) depends on \( Cl/V_D \). In practice, both \( Cl \) and \( k \) are dependent on various physiologic factors, such as blood flow, drug metabolism, renal secretion, and drug reabsorption. Most biologic events are the result of many events that are described more aptly as mutually interacting rather than acting independently. Thus, the underlying elimination process may be adequately described as fraction of drug removed per minute (\( k \)) or as volume of fluid removed per minute (\( Cl \)).

3. What is the difference between drug clearance and creatinine clearance?

**Answer:** With most drugs, total body clearance (often termed "clearance") is the sum of renal and nonrenal clearances. Creatinine is an endogenous marker that accumulates in the blood when renal function is impaired. Creatinine is excreted by glomerular filtration and is not reabsorbed. Creatinine clearance is a measure of glomerular filtration rate. Renal clearance is therefore proportional to creatinine
clearance but not equal to it, since most drugs are reabsorbed to some extent, and some drugs are actively secreted.

4. Theophylline is effective in the treatment of bronchitis at a blood level of 10-20 g/mL. At therapeutic range, theophylline follows first-order kinetics. The average $t_{1/2}$ is 3.4 hours, and the range is 1.8 to 6.8 hours. The average volume of distribution is 30 L.

a. What are the average, upper, and lower clearance limits for theophylline?

b. The renal clearance of theophylline is 0.36 L/hr. What are the $k_m$ and $k_e$, assuming all nonrenal clearance (Cl NR) is due to metabolism?

Answer:

a. 

$$CL_T = VDk = VD \frac{0.693}{t_{1/2}}$$

Average $CL_T = \frac{(30) \times (0.693)}{3.4} = 6.11$ L/hr

Upper $CL_T$ limit = $\frac{(30) \times (0.693)}{1.8} = 11.55$ L/hr

Lower $CL_T$ limit = $\frac{(30) \times (0.693)}{6.8} = 3.06$ L/hr

b. $CL_R = k_e VD = 0.36$ L/hr

$$k_e = \frac{0.36}{30} = 0.012 \text{ hr}^{-1}$$

$$CL_{nr} = CL_T - CL_r$$

$CL_{nr} = 6.11 - 0.36 = 5.75$ L/hr

$$CL_{nr} = k_m VD$$

$$k_m = \frac{5.75}{30} = 0.192 \text{ hr}^{-1}$$
4. A single 250-mg oral dose of an antibiotic is given to a young man (age 32 years, creatinine clearance 122 mL/min, 78 kg). From the literature, the drug is known to have an apparent V D equal to 21% of body weight and an elimination half-life of 2 hours. The dose is normally 90% bioavailable. Urinary excretion of the unchanged drug is equal to 70% of the absorbed dose.

a. What is the total body clearance for this drug?

b. What is the renal clearance for this drug?

c. What is the probable mechanism for renal clearance of this drug?

Answer:

\[
\text{a. Apparent V}_D = (0.21) (78,000 \text{ mL}) = 16,380 \text{ mL}
\]

\[
\text{Cl}_T = kV_D
\]

\[
\text{Cl}_T = \left(\frac{0.693}{2}\right) (16,380)
\]

\[
\text{Cl}_T = 5676 \text{ mL/hr} = 94.6 \text{ mL/min}
\]

\[
\text{b. } k_e = 70\% \text{ of the elimination constant}
\]

\[
k_e = (0.7)\left(\frac{0.693}{2}\right) = 0.243 \text{ hr}^{-1}
\]

\[
\text{Cl}_R = k_eV_D
\]

\[
\text{Cl}_R = (0.243) (16,380) = 3980 \text{ mL/hr} = 66.3 \text{ mL/min}
\]

c. Normal GFR = creatinine clearance = 122 mL/min

\[
\text{Cl}_R \text{ of drug} = 66.3 \text{ mL}
\]

Because the \text{Cl}_R of the drug is less than the creatinine clearance, the drug is filtered at the glomerulus and is partially reabsorbed.
5. A drug with an elimination half-life of 1 hour was given to a male patient (80 kg) by intravenous infusion at a rate of 300 mg/hr. At 7 hours after infusion, the plasma drug concentration was 11 g/mL.

a. What is the total body clearance for this drug?

b. What is the apparent \( V_D \) for this drug?

c. If the drug is not metabolized and is eliminated only by renal excretion, what is the renal clearance of this drug?

d. What is the probable mechanism for renal clearance of this drug?

**Answer:**

a. During intravenous infusion, the drug levels will reach more than 99% of the plasma steady-state concentration after seven half-lives of the drug.

\[
Cl_T = \frac{R}{C_{SS}} = \frac{300,000 \, \mu g/hr}{11 \, \mu g/mL} = 27,272 \, mL/hr
\]

b. \( Cl_T = kV_D \)

\[
V_D = \frac{27,272}{0.693} = 39,354 \, mL
\]

c. Since \( k_m = 0 \quad k_e \approx k \)

\[
Cl_T = Cl_R = 27,272 \, mL/hr
\]

d. \( Cl_R = 27,272 \, mL/hr = 454 \, mL/min \)

Normal GFR is 100–130 mL/min. The drug is probably filtered and actively secreted in the kidney.

5. In order to rapidly estimate the renal clearance of a drug in a patient, a 2-hour postdose urine sample was collected and found to contain 200 mg of drug. A midpoint plasma sample was taken (1 hr postdose) and the drug concentration in plasma was found to be 2.5 mg%. Estimate the renal clearance for this drug in the patient.
Answer:

\[ Cl_R = \frac{\text{excretion rate}}{C_p} = \frac{200 \text{ mg/2 hr}}{2.5 \text{ mg/100 mL}} \]
\[ Cl_R = 4000 \text{ mL/hr} \]

6. According to the manufacturer, after the antibiotic cephradine (Velosef), given by IV infusion at rate of 5.3 mg/kg per hour to 9 adult male volunteers (average weight, 71.7 kg), a steady-state serum concentration of 17 g/mL was measured. Calculate the average total body clearance for this drug in adults.

Answer:

\[ Cl_T = \frac{R}{C_{ss}} \]
\[ Cl_T = \frac{5.3 \text{ mg/kg hr}}{17 \text{ mg/L}} = 0.312 \text{ L/kg hr} \]

For a 71.7-kg adult,
\[ Cl_T = (0.312 \text{ L/kg hr})(71.7 \text{ kg}) = 22.4 \text{ L/hr} \]

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