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Drug Elimination

Drugs are removed from the body by various elimination processes. *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 drugs are excreted mainly by renal excretion, a process in which the drug passes through the kidney to the bladder and ultimately into the urine. 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 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. Biotransformation is usually an enzymatic process. A few drugs may also be changed chemically by a nonenzymatic process (eg, ester hydrolysis). The enzymes involved in the biotransformation of drugs are located mainly in the liver (). Other tissues such as kidney, lung, small intestine, and skin also contain biotransformation enzymes.

Drug elimination in the body involves many complex rate processes. Although organ systems have specific functions, the tissues within the organs are not structurally homogeneous, and elimination processes may vary in each organ. In , elimination was modeled by an overall first-order elimination rate process. In this chapter, 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. For example, clearance considers that a certain portion or percent of the distribution volume is cleared of drug over a given time period. This basic concept (also see) will be elaborated upon after a review of the anatomy and physiology of the kidney.

The Kidney

The liver (see) and kidney are the two major drug elimination organs in the body, though drug elimination can also occur almost anywhere in the body. 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. To maintain salt and water balance, the kidney excretes excess electrolytes, water, and waste products while conserving solutes necessary for proper body function. In addition, the kidney has two endocrine functions: (1) secretion of renin, which regulates blood pressure; and (2) secretion of erythropoietin, which stimulates red blood cell production.

Anatomic Considerations

The kidneys are located in the peritoneal cavity. A general view is shown in and a longitudinal view in . The outer zone of the kidney is called the *cortex*, and the inner region is called the *medulla*. The *nephrons* are the basic functional units, collectively responsible for the removal of metabolic waste and the maintenance of water and electrolyte balance. Each kidney contains 1 to 1.5 million nephrons. The *glomerulus* of each nephron starts in the cortex. *Cortical nephrons* have short *loops of Henle* that remain exclusively in the cortex; *juxtamedullary nephrons* have long loops of Henle that extend into the medulla (). The longer loops of Henle allow for a greater ability of the nephron to reabsorb water, thereby producing a more concentrated urine.

Figure 6-1.
The general organizational plan of the urinary system. ()

Figure 6-2.

Longitudinal section of the kidney, illustrating major anatomical features and blood vessels.
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Figure 6-3.

Cortical and juxtamedullary nephrons and their vasculature.
()

Blood Supply

The kidneys represent about 0.5% of the total body weight and receive approximately 20–25% of the cardiac output. The kidney is supplied by blood via the renal artery, which subdivides into the interlobar arteries penetrating within the kidney and branching farther into the afferent arterioles. Each afferent arteriole carries blood toward a single nephron into the glomerular portion of the nephron (*Bowman's capsule*). The filtration of blood occurs in the glomeruli in Bowman's capsule. From the capillaries (*glomerulus*) within Bowman's capsule, the blood flows out via the efferent arterioles and then into a second capillary network that surrounds the tubules (*peritubule capillaries* and *vasa recti*), including the loop of Henle, where some water is reabsorbed.

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

where Hct is hematocrit.

Hct is the fraction of blood cells in the blood, about 45% of the total blood volume, or 0.45. The relationship of renal blood flow to renal plasma flow is given by a rearrangement of Equation 6.1:

Assuming a hematocrit of 0.45 and a RBF of 1.2 L/min, using the above equation, RPF = 1.2 – (1.2 x 0.45) = 0.66 L/min or 660 mL/min, approximately 950 L/day. The *glomerular filtration rate* (GFR) is about 125 mL/min in an average adult, or about 20% of the RPF. The ratio GFR/RPF is the *filtration fraction*.

Regulation of Renal Blood Flow

Blood flow to an organ is directly proportional to the arteriovenous pressure difference (*perfusion pressure*) across the vascular bed and indirectly proportional to the vascular resistance. The normal renal arterial pressure () is approximately 100 mmHg and falls to approximately 45–60 mm Hg in the glomerulus (glomerular capillary hydrostatic pressure). This pressure difference is probably due to the increasing vasculature resistance provided by the small diameters of the capillary network. Thus, the GFR is controlled by changes in the glomerular capillary hydrostatic pressure.

Figure 6-4.

Approximate pressures at different points in the vessels and tubules of the functional nephron and in the interstitial fluid.
()

In the normal kidney, RBF and GFR remain relatively constant even with large differences in mean systemic blood pressure (). The term *autoregulation* refers to the maintenance of a constant blood flow in the presence of large fluctuations in arterial blood pressure. Because autoregulation maintains a relatively constant blood flow, the filtration fraction (GFR/RPF) also remains fairly constant in this pressure range.

Figure 6-5.

Schematic representation of the effect of mean arterial pressure on GFR and RPF, illustrating the phenomenon of

autoregulation.
()

Glomerular Filtration and Urine Formation

A normal adult male subject has a GFR of approximately 125 mL/min. About 180 L of fluid per day are filtered through the kidneys. In spite of this large filtration volume, the average urine volume is 1–1.5 L. Up to 99% of the fluid volume filtered at the glomerulus is reabsorbed. Besides fluid regulation, the kidney also regulates the retention or excretion of various solutes and electrolytes (). With the exception of proteins and protein-bound substances, most small molecules are filtered through the glomerulus from the plasma. The filtrate contains some ions, glucose, and essential nutrients as well as waste products, such as urea, phosphate, sulfate, and other substances. The essential nutrients and water are reabsorbed at various sites, including the proximal tubule, loops of Henle, and distal tubules. Both active reabsorption and secretion mechanisms are involved. The urine volume is reduced, and the urine generally contains a high concentration of metabolic wastes and eliminated drug products.

Table 6.1 Quantitative Aspects of Urine Formation[a]

	Per 24 Hours				
Substance	**Filtered**	**Reabsorbed**	**Secreted**	**Excreted**	**Percent Reabsorbed**
Sodium ion (mEq)	26,000	25,850		150	99.4
Chloride ion (mEq)	18,000	17,850		150	99.2
Bicarbonate ion (mEq)	4,900	4,900		0	100
Urea (mM)	870	460[b]		410	53
Glucose (mM)	800	800		0	100
Water (mL)	180,000	179,000		1,000	99.4
Hydrogen ion			Variable	Variable[c]	
Potassium ion (mEq)	900	900[d]	100	100	100[d]

[a]Quantity of various plasma constituents filtered, reabsorbed, and excreted by a normal adult on an average diet.
[b]Urea diffuses into, as well as out of, some portions of the nephron.
[c]pH or urine is on the acid side (4.5–6.9) when all bicarbonate is reabsorbed.
[d]Potassium ion is almost completely reabsorbed before it reaches the distal nephron. The potassium ion in the voided urine is actively secreted into the urine in the distal tubule in exchange for sodium ion.
From , with permission.

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

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.

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. For example, 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. Active secretion is extremely rapid for these drugs, and practically all the drug carried to the kidney is eliminated in a single pass. 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.

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 pK_a of the drug. Both of these factors together determine the percentage of dissociated (ionized) and undissociated (nonionized) drug. Generally, the undissociated species is more lipid soluble (less water soluble) and has greater membrane permeability. The undissociated drug is easily reabsorbed from the renal tubule back into the body. This process of drug reabsorption can significantly reduce the amount of drug excreted, depending on the pH of the urinary fluid and the pK_a of the drug. The pK_a 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 or diets rich in carbohydrates 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, when administered in large quantities. By far the most important changes in urinary pH are caused by fluids administered intravenously. 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–Hesselbalch equation*.

Rearrangement of this equation yields

The fraction or percent of weak acid drug ionized in any pH environment may be calculated with Equation 6.5. For acidic drugs with pK_a values from 3 to 8, a change in urinary pH affects the extent of dissociation (). The extent of dissociation is more greatly affected by changes in urinary pH for drugs with a pK_a of 5 than with a pK_a of 3. Weak acids with pK_a values of less than 2 are highly ionized at all urinary pH values and are only slightly affected by pH variations.

Table 6.2 Effect of Urinary pH and pK_a on the Ionization of Drugs

pH of Urine	**Percent of Drug Ionized: pK_a=3**	**Percent of Drug Ionized: pK_a=5**
7.4	100	99.6
5	99	50.0
4	91	9.1
3	50	0.99

For a weak base drug, the Henderson–Hasselbalch equation is given as

and

The greatest effect of urinary pH on reabsorption occurs with weak base drugs with pK_a values of 7.5–10.5.
From the Henderson–Hesselbalch 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,

For weak bases,

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 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.
Practice Problems
Let $pK_a = 5$ for an acidic drug. Compare the *U*/*P* at urinary pH **(a)** 3, **(b)** 5, and **(c)** 7.
Solution
a. At pH = 3,

b. At pH = 5,

c. At pH = 7,

In addition to the pH of the urine, the rate of urine flow influences the amount of filtered drug that is reabsorbed. The normal flow of urine is approximately 1–2 mL/min. Nonpolar and nonionized drugs, which are normally well reabsorbed in the renal tubules, are sensitive to changes in the rate of urine flow. Drugs that increase urine flow, such as ethanol, large fluid intake, and methylxanthines (such as caffeine or theophylline), decrease the time for drug reabsorption and promote their excretion. Thus, forced diuresis through the use of diuretics may be a useful adjunct for removing excessive drug in an intoxicated patient, by increasing renal drug excretion.
Drug Clearance
Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process. Drug clearance (*body clearance, total body clearance*, or Cl_T) considers the entire body as a single drug-eliminating system from which many unidentified elimination processes may occur. Instead of describing the drug elimination rate in terms of amount of drug removed per time unit (eg, mg/min), drug clearance is described in terms of volume of fluid clear of drug per time unit (eg, mL/min).
There are several definitions of clearance, which are similarly based on volume of drug removed per unit time. The simplest concept of clearance regards the body as a space that contains a definite volume of body fluid (apparent volume of distribution, V_D) in which the drug is dissolved. Drug clearance is defined as the fixed volume of fluid (containing the drug) cleared of drug per unit of time. The units for clearance are volume/time (eg, mL/min, L/hr).
For example, if the Cl_T 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 cleared of drug per minute.
Alternatively, Cl_T 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.

where D_E is the amount of drug eliminated and dD_E/dt is the rate of elimination.
Rearrangement of Equation 6.11 gives Equation 6.12.

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, as shown in Equation 6.10.
As discussed in previous chapters, a first-order elimination rate, dD_E/dt, is equal to kD_B or kC_pV_D. Based on Equation 6.10, substituting elimination rate for kC_pV_p,

Equation 6.13 shows that clearance is the product of V_D and k, both of which are constant. As the plasma drug concentration decreases during elimination, the rate of drug elimination, dD_E/dt, decreases accordingly, but clearance remains constant. Clearance is constant as long as the rate of drug elimination is a first-order process.

Example

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

C_p, is 2 g/mL.

Solution

Elimination rate = C_p x Cl_T (from Eq. 6.12)

Using the previous penicillin example, assume that the plasma penicillin concentration is 10 g/mL. From Equation 6.11, the rate of drug elimination is

Thus, 150 g/min of penicillin is eliminated from the body when the plasma penicillin concentration is 10 g/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 g/min when the plasma penicillin concentration was

10 g/mL, then the clearance of penicillin is calculated from Equation 6.11:

Just as the elimination rate constant (k) represents the sum total of all the rate constants for drug elimination, including excretion and biotransformation, Cl_T is the sum total of all the clearance processes in the body, including clearance through the kidney (renal clearance), lung, and liver (hepatic clearance).

From Equation 6.14, body clearance Cl_T of a drug is the product of two constants, k and V_D, which reflect all the distribution and elimination processes of the drug in the body. The volume of distribution and elimination rate constant are affected by blood flow, which will be considered below (and in) using a physiologic model.

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

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 6.13.

For a 70-kg patient,

Clearance Models

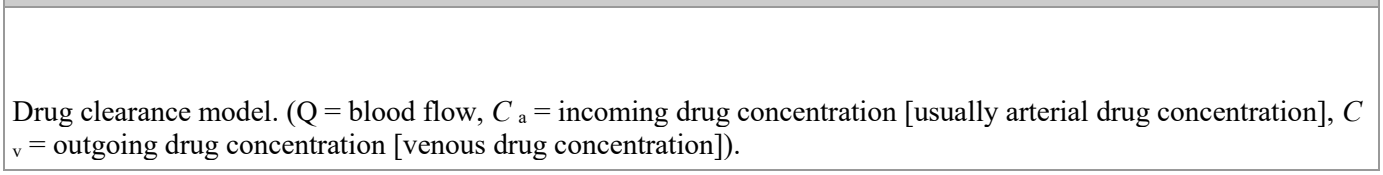
The calculation of clearance from k and V_D assumes (sometimes incorrectly) a defined model, whereas clearance estimated directly from the plasma drug concentration time curve does not assume any model. Although clearance may be regarded as the product of k and V_D, Equation 6.10 is far more general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

Physiologic/Organ Clearance

Clearance may be calculated for any organ involved in the irreversible removal of drug from the body. Many organs in the body have the capacity for drug elimination, including drug excretion and biotransformation. The kidneys and

liver are the most common organs involved in excretion and metabolism, respectively. Physiologic pharmacokinetic models are based on drug clearance through individual organs or tissue groups ().

Figure 6-6.



Drug clearance model. (Q = blood flow, C_a = incoming drug concentration [usually arterial drug concentration], C_v = outgoing drug concentration [venous drug concentration]).

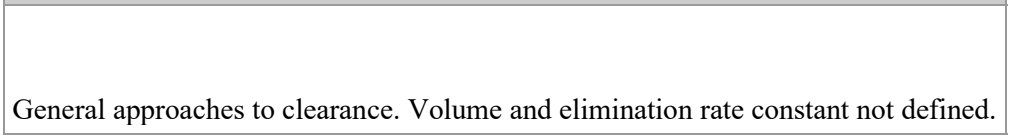
For any organ, clearance may be defined as the fraction of blood volume containing drug that flows through the organ and is eliminated of drug per unit time. From this definition, clearance is the product of the blood flow (Q) to the organ, and the extraction ratio (ER). The ER is the fraction of drug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

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 (). The ER is $C_a - C_v$ divided by the entering drug concentration (C_a), as shown in Equation 6.16.

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). An ER of 0.25 indicates that 25% of the incoming drug concentration is removed by the organ as the drug passes through.
Substituting for ER into Equation 6.15 yields

The physiologic approach to clearance shows that clearance depends on the blood flow rate and the ability of the organ to eliminate drug, whereas the classical definitions of clearance is that a constant or static fraction of the volume in which the drug is contained is removed per unit time by the organ. However, clearance measurements using the physiologic approach require invasive techniques to obtain measurements of blood flow and extraction ratio. The physiologic approach has been used to describe hepatic clearance, which is discussed under hepatic elimination (). More classical definitions of clearance have been applied to renal clearance because direct measurements of plasma drug concentration and urinary drug excretion may be obtained. The various approaches for estimating clearance are described in .

Figure 6-7.



General approaches to clearance. Volume and elimination rate constant not defined.

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 *noncompartment* model approaches used to calculate certain pharmacokinetic parameters such as clearance and bioavailability (F). The major advantage of model-independent methods is that no assumption for a specific compartment model is required to analyze the data. Moreover, the volume of distribution and the elimination rate constant need not be determined directly from the equation that best fits the plasma drug concentration–time curve.
Clearance can be determined directly from the plasma–time concentration curve by

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 noncompartment approach, the general equation uses area under the curve of the plasma drug concentration curve, $[AUC]^{\infty}_0$ for the calculation of clearance.

Because $[AUC]^{\infty}_{0}$ 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 $[AUC]^{\infty}_{t}$ or (C_{pt}/k), first-order elimination is usually assumed. This calculation of Cl_T is referred to as a noncompartment 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.

Renal Clearance

Renal clearance, 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).

An alternative approach to obtaining Equation 6.20 is to consider the mass balance of drug cleared by the kidney and ultimately excreted in the urine. For any drug cleared through the kidney, the rate of the drug passing through kidney (via filtration, reabsorption, and/or active secretion) must equal the rate of drug excreted in the urine.

Rate of drug passing through kidney = rate of drug excreted

where 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 6.21 gives

because the excretion rate = $Q_u C_u = dD_u/dt$, Equation 6.22 is the equivalent of Equation 6.20.

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:

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 (). However, further renal drug excretion studies are necessary to confirm unambiguously the mechanism of excretion.

Table 6.3 Comparison of Clearance of a Sample Drug to Clearance of a Reference Drug, Inulin

Clearance Ratio	**Probable Mechanism of Renal Excretion**
	Drug is partially absorbed
	Drug is filtered only
	Drug is actively secreted

A method to quantify renal drug excretion is to consider the kinetic nature of the elimination processes. For this consideration, some of the detailed steps in the elimination process may be omitted or simplified. For example, assume that the body fluid volume is the V_D and that the plasma drug concentration, C_p, is changing after an intravenous bolus injection.

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 x GFR (). 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.

Table 6.4 Urinary Drug Excretion Rate[a]

Time (min)	**C_p (g/ml)**	**Excretion Rate (g/min) (Drug Filtered by GFR per min)**

0	$(C_p)_0$	$(C_p)_0$ x 125
1	$(C_p)_1$	$(C_p)_1$ x 125
2	$(C_p)_2$	$(C_p)_2$ x 125
t	$(C_p)_t$	$(C_p)_t$ = 125

[a]Assumes that the drug is excreted by filtration only and that the GFR is 125 mL/min.
Note that the quantity of drug excreted per minute is always the plasma concentration (C_p) multiplied by a constant (eg, 125 mL/min), which in this case is also the renal clearance for the drug. The glomerular filtration rate may be treated as a first-order process relating to C_p. The rate of drug excretion using a compartment approach and physiologic approach are compared in Equations 6.22 and 6.23.

Equating 6.24 with 6.25,

Equation 6.26 shows that, in the absence of other processes of drug elimination, the excretion rate constant is a fractional constant reflecting the volume pumped out per unit time due to GFR relative to the volume of the body compartment (V_D).
In the one-compartment model, a drug is assumed to be uniformly and instantly equilibrated. However, the renal plasma drug concentration entering the kidney (arterial drug concentration) is always higher than the venous plasma drug concentration leaving the kidney. In spite of this inconsistency, the rate of drug elimination is properly adjusted in the estimation of the first-order elimination rate constant (k) given in Equation 6.25 if the overall plasma drug concentration profile is adequately described. If the pharmacokinetic parameters are properly calculated to fit the data, the parameters k and V_D reflect the underlying kinetic processes.
Filtration and Reabsorption
For a drug with a *reabsorption fraction* of *fr*, the drug excretion rate is reduced, and Equation 6.25 is restated as Equation 6.27:

Equating the right sides of Equations 6.27 and 6.24 indicates that the first-order rate constant (k_e) in the compartment model is equivalent to $Cl_R (1 - fr)/V_D$. 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 (). Clearance decreases because the total excretion rate of the drug increases to the point where it is approximately equal to the filtration rate ().

Figure 6-8.

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 6-9.

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.

The power of the kinetic approach is that, even lacking any knowledge of GFR, active secretion, or the reabsorption

process, modeling the data allows the process of drug elimination to be described quantitatively. If a change to a higher-order elimination rate process occurs, then an additional process besides GFR may be involved. The compartmental analysis aids the ultimate development of a model consistent with physiologic functions of the body.
Example
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 6.17 results in

Interestingly, known drug clearance tells little about the dosing differences of the two drugs, although it helps to identify the mechanism of drug elimination. In this example, both drugs have the same clearance.
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.

Here k specifies the fraction of drug eliminated regardless of distributional differences of the drug.
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. 6.28). For a drug that is excreted rapidly, dD_u/dt is large, the slope is steeper, and clearance is greater (, line *A*). For a drug that is excreted slowly through the kidney, the slope is smaller (, line *B*).

Figure 6-10.
Rate of drug excretion versus concentration of drug in the plasma. Drug A has a higher clearance than drug B, as shown by the slopes of line *A* and line *B*.

From Equation 6.20,

Multiplying both sides by C_p gives

By rearranging Equation 6.28 and integrating, one obtains

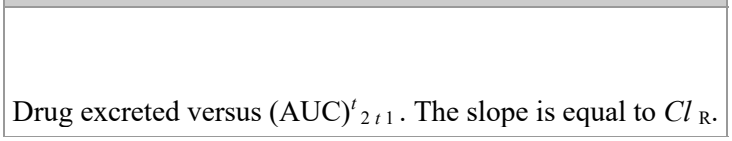
A graph is then plotted of cumulative drug excreted in the urine versus the area under the concentration–time curve (). Renal clearance is obtained from the slope of the curve. The area under the curve can be estimated by the trapezoidal rule or by other measurement methods. The disadvantage of this method is that if a data point is missing, the cumulative amount of drug excreted in the urine is difficult to obtain. However, if the data are complete, then the determination of clearance is more accurate by this method.

Figure 6-11.
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, $[D_u]^{t_2}_{t_1}$ versus $[AUC]^{t_2}_{t}$, one obtains an equation similar to that presented previously:

The slope is equal to the renal clearance ().

Figure 6-12.



Drug excreted versus $(AUC)^{t}_{2\,t\,1}$. The slope is equal to Cl_R.

Model-Independent Methods

Clearance rates may also be estimated by a single (nongraphical) calculation from knowledge of the $[AUC]^{\infty}_{0}$, the total amount of drug absorbed, FD_0, and the total amount of drug excreted in the urine, D^{∞}_{u}. For example, if a single IV bolus drug injection is given to a patient and the $[AUC]^{\infty}_{0}$ is obtained from the plasma drug level–time curve, then total body clearance is estimated by

If the total amount of drug excreted in the urine, D^{∞}_{u} has been obtained, then renal clearance is calculated by

The calculations using Equations 6.33 and 6.34 allow for rapid and easily obtainable estimates of drug clearance. However, only a single dose estimate is obtained; therefore, the calculations do not reflect nonlinear changes in the clearance rates, as indicated in .

Clearance can also be calculated from fitted parameters. If the volume of distribution and elimination constants are known, body clearance (Cl_T), renal clearance (Cl_R), and hepatic clearance (Cl_h) can be calculated according to the following expressions:

Total body clearance (Cl_T) is equal to the sum of renal clearance and hepatic clearance and is based on the concept that the entire body acts as a drug-eliminating system.

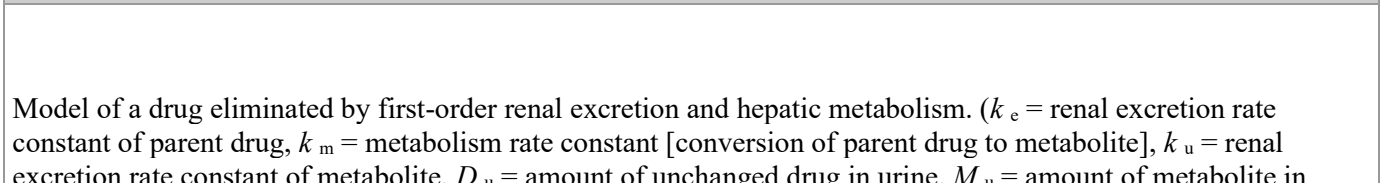
By substitution of Equations 6.35 and 6.36 into Equation 6.38,

Dividing by V_D on both sides of Equation 6.39,

Practice Problem

Consider a drug that is eliminated by first-order renal excretion and hepatic metabolism. The drug follows a one-compartment model and is given in a single intravenous or oral dose (). Working with the model presented in , assume that a single dose (100 mg) of this drug is given orally. The drug is 90% systemically available. The total amount of unchanged drug recovered in the urine is 60 mg, and the total amount of metabolite recovered in the urine is 30 mg (expressed as milligram equivalents to the parent drug). According to the literature, the elimination half-life for this drug is 3.3 hours and its apparent volume of distribution is 1000 mL. From the information given, find **(a)** the total body clearance, **(b)** the renal clearance, and **(c)** the nonrenal clearance of the drug.

Figure 6-13.



Model of a drug eliminated by first-order renal excretion and hepatic metabolism. (k_e = renal excretion rate constant of parent drug, k_m = metabolism rate constant [conversion of parent drug to metabolite], k_u = renal excretion rate constant of metabolite, D_u = amount of unchanged drug in urine, M_u = amount of metabolite in urine, C_m = plasma concentration of the metabolite, C_p = plasma concentration of the parent drug, V_D = apparent volume of distribution of parent drug, V_m = apparent volume of distribution of metabolite.)

Solution

a. Total body clearance:

b. Renal clearance. First find k_e:

Then, from Equation 6.36,

c. Nonrenal clearance:

Alternatively,

Applying Equation 6.37,

Calculation of Clearance in Multicompartmental Models
Clearance is a direct measure of elimination from the central compartment, regardless of the number of compartments. The central compartment consists of the plasma and highly perfused tissues in which drug equilibrates rapidly (). The tissues for drug elimination, namely kidney and liver, are considered integral parts of the central compartment.
The first-order elimination rate constant k is a useful measurement for drug elimination in a one-compartment model and can be calculated after IV bolus (), IV infusion (), or even oral () or multiple doses () using plasma drug concentrations. The value of k can also be calculated by measuring D_u, drug excreted into the urine (and below).
In multicompartment models, several methods for the estimation of clearance are possible. The overall elimination rate constant k represents elimination from the central compartment, and total body clearance is the product of k times the volume of the central compartment, V_p.
For the two-compartment model, total body clearance may be estimated according to Equation 6.42 as the product

by the elimination rate constant b times V_D . This latter method gives the same value for clearance. Other methods for calculating total body clearance consider either instantaneous clearance or steady-state clearance, depending on which volume of distribution is chosen. Generally, the various calculations of total body clearance for drugs characterized by multicompartment pharmacokinetics are useful for comparison purposes. For the two-compartment model drug, body clearance can be calculated with the following equation:

or, alternatively,

To obtain renal clearance for drugs demonstrating two-compartment kinetics with metabolism and excretion, the following equation is used:

Fraction of Drug Excreted
For many drugs, the total amount of unchanged drug excreted in the urine D^{∞}_u, may be obtained by direct assay. The ratio of D^{∞}_u, to the fraction of the dose absorbed, FD_0, is equal to the fraction of drug excreted unchanged in the urine and is also equal to k_e/k.

Renal clearance may be determined from the fraction of unchanged drug excreted in the urine and the total body clearance.

Equation 6.46 can also be expressed as

Practice Problem
An antibiotic is given by IV bolus injection at a dose of 500 mg. The apparent 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_e, Cl_T, Cl_R, and Cl_h.
Solution
Since the elimination half-life, $t_{1/2}$, for this drug is 6 hours, a urine collection for 48 hours represents 8 x $t_{1/2}$, which allows for greater than 99% of the drug to be eliminated from the body. The fraction of drug excreted unchanged in the urine, f_e, is obtained by using Equation 6.47 and recalling that $f = 1$ for drugs given by IV bolus injection.

Therefore, 80% of the absorbed dose is excreted in the urine unchanged. Calculations for k, k_e, Cl_T, Cl_R, and Cl_h are given here:

Alternatively,

Protein-Bound Drugs

Protein-bound drugs are not eliminated by glomerular filtration. Therefore, Equation 6.18 for the calculation of renal clearance must be modified, because only the free drug is excreted by a linear process. The bound drugs are usually excreted by active secretion, following capacity-limited kinetics. The determination of clearance that separates the two components results in a hybrid clearance. There is no simple way to overcome this problem. Clearance values for a protein-bound drug is therefore calculated with the following equation:

In practice, this equation is not easily applied because the rate of drug excretion is usually determined after collecting urine samples. The drug excreted in the urine is the sum of drug excreted by active tubular secretion and by passive glomerular filtration, minus drug that is reabsorbed. However, it is not possible to distinguish the amount of bound drug actively secreted or reabsorbed from the amount of drug excreted by glomerular filtration. Equation 6.48 can be used for drugs that are protein bound but not actively secreted. Nonlinear drug binding makes clearance less useful due to model complication.

Equation 6.48 is also used in the calculation of free drug concentration in the plasma, where is the fraction of

bound drug and 1 – is the fraction of free drug.

For most drug studies, the total plasma drug concentration (free plus bound drug) is used in clearance calculations. If renal clearance is corrected for the fraction of drug bound to plasma proteins using Equation 6.48, then the renal clearance for the free drug concentration may have a higher value compared to the uncorrected renal clearance using the total plasma drug concentrations.

Plasma protein binding has very little effect on the renal clearance of actively secreted drugs such as penicillin. For these drugs, the free drug fraction is filtered at the glomerular, whereas the protein-bound drug appears to be stripped from the binding sites and actively secreted into the renal tubules.

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. From Equation 6.35 we obtain

and

Therefore, by substitution,

From Equation 6.50, as Cl_T decreases, which might happen in the case of renal insufficiency, the $t_{1/2}$ for the drug increases. A good relationship of V_D, k, and $t_{1/2}$ is shown in .

Table 6.5 Relationships of Clearance, Rate Constant of Elimination, and Elimination Half-Life

	K_e and $t_{1/2}$ in Various Media of Distribution		
Clearance[a]	**Plasma Water (3,000 mL)**	**Extracellular Fluid (12,000 mL)**	**Body Water (41,000 mL)**
Partial reabsorption (eg, 30 mL/min)	1.00×10^{-2} (69 min)	2.50×10^{-3} (277 min)	7.32×10^{-4} (947 min)
Glomerular filtration (eg, 130 mL/min)	4.33×10^{-2} (16 min)	1.08×10^{-2} (64 min)	3.17×10^{-3} (219 min)

Tubular secretion (eg, 650 mL/min)	2.17×10^{-1} (3 min)	5.42×10^{-2} (13 min)	1.59×10^{-2} (44 min)

[a]Entries are values for k_e, the rate constant of elimination (in units of min^{-1}); parenthetic entries are corresponding values of the elimination half-life. The clearance given under "partial reabsorption" is arbitrary; any clearance between 0 (complete reabsorption) and 650 mL/min is possible.
From , with permission.
Total body clearance, Cl_T, is a more useful index of measurement of drug removal compared to the elimination half-life, $t_{1/2}$. Total body clearance takes into account changes in both the apparent volume of distribution, V_D, and $t_{1/2}$. In overt obesity or edematous conditions, the V_D may change without a marked change in $t_{1/2}$. As will be shown in and , V_D is important in the calculation of the loading dose, whereas Cl_T is important in the calculation of the maintenance dose.
Total body clearance may be calculated by the ratio, $FD_0/[AUC]^{\infty}_0$, which is considered a model-independent method and assumes no particular pharmacokinetic model for drug elimination.

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:

where C_{SS} is the steady-state plasma drug concentration and R is the rate of infusion. Equation 6.52 is valid for drugs that follow either the one- or the two-compartment open model (see).
Practice Problems
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?
Solution

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?
Solution

In patients with renal impairment the $t_{1/2}$ generally changes more drastically than the V_D. The clearance given under partial reabsorption in is arbitrary; any clearance between 0 (complete reabsorption) and 650 mL/min is possible.
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?
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?
3. What is the difference between drug clearance and creatinine clearance?
Learning Questions
1. Explain why plasma protein binding will prolong the renal clearance of a drug that is excreted only by glomerular filtration but does not affect the renal clearance of a drug excreted by both glomerular filtration and active tubular secretion.
2. Explain the effect of alkalization or acidification of the urine on the renal clearance of dextroamphetamine sulfate. Dextroamphetamine sulfate is a weak base with a pK_a of 9.4.

3. 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?
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?
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?
6. 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.
7. 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.
8. Cephradine is completely excreted unchanged in the urine, and studies have shown that probenecid given concurrently causes elevation of the serum cephradine concentration. What is the probable mechanism for the interaction of probenecid with cephradine?
9. Why is clearance used as a measurement of drug elimination, rather than the excretion rate of the drug?
10. What is the advantage of using total body clearance as a measurement of drug elimination compared to using the elimination half-life of the drug?
11. A patient was given 2500 mg of a drug by IV bolus dose, and periodic urinary data was collected. **(a)** Determine the renal clearance of the drug using urinary data. **(b)** Determine total body clearance using the area method. **(c)** Is there any nonrenal clearance of the drug in this patient? What would be the nonrenal clearance, if any? How would you determine clearance using a compartmental approach and compare that with the area method?

Time (hr)	**Plasma Urinary Concentration (g/mL)**	**Urinary Volume (mL)**	**UrinaryConcentration (g/mL)**
0	250.00	100.00	0.00
1	198.63	125.00	2880.00
2	157.82	140.00	1901.20
3	125.39	100.00	2114.80
4	99.63	80.00	2100.35
5	79.16	250.00	534.01
6	62.89	170.00	623.96
7	49.97	160.00	526.74
8	39.70	90.00	744.03
9	31.55	400.00	133.01
10	25.06	240.00	176.13

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