EXCRETION OF DRUGS

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. Drug excretion is divided into two types.

1. **Renal excretion:** In this process drug passes through the kidney to the bladder and ultimately into the urine. Non-volatile drugs are excreted mainly by renal excretion.

2. **Non renal excretion:** Excretion by organs other than kidneys is known as nonrenal excretion. The other organs involved in the excretion of drugs are:

- Lungs
- Biliary system
- Intestine
- salivary glands
- Genital system
- Mammary gland
- Skin/sweat gland

RENAL DRUG EXCRETION

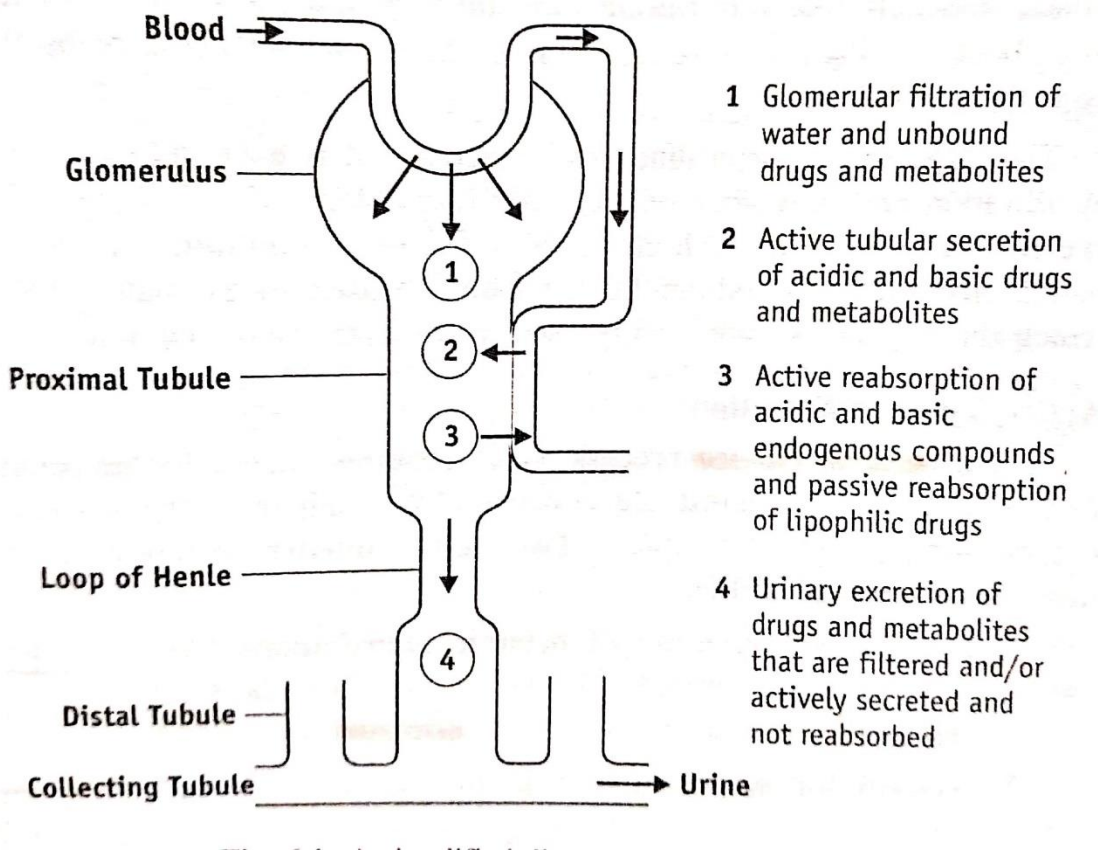
Renal excretion is a major route of elimination for many drugs. Drugs those are excreted from renal excretion are-

1. Water soluble
2. Non-soluble
3. Small in molecular size (less than 500 Daltons)
4. The ones that are metabolized slowly.

The basic functional unit of kidney involved in excretion is the nephron. Each kidney comprises of one million nephrons. Each nephron is made up of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule and the collecting tubule.

The principle processes that determine the urinary excretion of a drug are-

1. Glomerular filtration
2. Active tubular secretion
3. Active or passive tubular reabsorption



A simplified diagram illustrating processes involved in the urinary excretion of drugs

Glomerular filtration and active tubular secretion tend to increase the concentration of drugs in lumen and hence facilitate excretion whereas tubular reabsorption decreases it and prevents the movement of drug out of the body. Thus, the rate of excretion can be given by equation:

Rate of excretion = Rate of Filtration + Rate of Secretion – Rate of Reabsorption

Glomerular Filtration

- Glomerular filtration is a unidirectional process that occurs for most small molecules (MW < 500), including nonionized and ionized drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus.
- The glomerulus also acts as a negatively charged selective barrier promoting retention of anionic compounds. The major driving force for the glomerular filtration is the hydrostatic pressure within the glomerular capillaries.
- Out of the 25% of cardiac output or 1.2 liters of blood/min that goes to the kidneys via renal artery, only 10 % or 120 to 130 ml/min is filtered through the glomeruli, the rate being called as the glomerular filtration rate (GFR).
- Though some 180 liters of protein and cell free ultra-filtrate pass through the glomeruli each day, only about 1.5 liters is excreted as urine, the remainder being reabsorbed from the tubules.

- The Glomerular filtration rate (GFR) is measured by using a drug that is eliminated by filtration only and is neither secreted nor reabsorbed in the tubules. Examples of such drugs are creatinine and inulin. Therefore 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 increases renal drug clearance for some drugs.

Active tubular secretion

- Active tubular secretion is an active transport process whereby drug diffuses from the blood capillaries to the renal tubular membrane.
- 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 a capacity limited and may be saturated.
- Two active renal secretion system have been identified:
    a) **Systems for secretion of weak acids/anions:** like penicillin, salisylates, glucuronides sulphates, etc. It is the same system by which endogenous acids such as uric acid are secreated.
    b) **Systems for secretion of weak bases/cations:** like morphine, mecamylamine, hexamethonium and endogenous amines such as catecholaminnes, choline, histamine etc.
- Both the systems are relatively non selective and independent of each other but both can be bidirectional. i.e. agents may both be secreted as well as reabsorbed actively, for example uric acid.
- Active secretion is unaffected by changes in pH and protein binding since the bound drug rapidly dissociates the moment the unbound drug gets excreted.
- Drugs undergoing active secretion have excretion rate values greater than the normal GFR value of 130 ml/min; for example penicillin has renal clearance value of 500 ml/min. Such a high value is indicative of both glomerular filtration as well as tubular secretion.
- Agents that are used to measure active tubular secretion are the ones that are filtered as well as secreted to such an extent that they are removed from the blood in a single pass through the kidneys i.e. their clearance reflects the renal plasma flow rate which is 600 to 700 ml/min.
- Two structurally similar drugs having similar ionic charge and employing the same carrier-mediated process for excretion enter into competition. A drug with greater rate of clearance will retard the excretion of the other drug with which it competes.

- The half-life of both the drug is increased since the total sites for active secretion are limited. This may result in accumulation of drugs and thus, results in toxicity.
- An interesting example of this is the anionic agent probenecid and penicillin. They have affinity for same carrier. When probenecid is given with penicillin, Probenecid inhibits the active tubular secretion of organic acids such as penicillins, thus increasing their concentration in plasma by at least two fold.
- A 50 % reduction in penicillin G dose is suggested, especially when the drug is meant to be consumed in large doses as in gonococcal infections.
- The actively secreted and filtered probenecid, if unionized in tubular field, is highly lipid-soluble and therefore will get reabsorbed passively. This reabsorption of probenecid thus suppress the carrier-mediated reabsorption of the endogenous metabolite, uric acid. Inhibition of reabsorption of uric acid increases the excretion of uric acid and thus it act as uricosuric agent in the treatment of gout.

Tubular Reabsorption

- Tubular reabsorption occurs after the glomerular filtration of drugs. It takes place all along the renal tubule. Reabsorption of a drug is indicated when the excretion rate values are less than the GFR of 130 ml/min.
- An agent such as glucose that is completely reabsorbed after filtration has a clearance value of zero. Reabsorption results in an increase in the half-life of a drug.

Tubular reabsorption can either be an:

1. Active process, or
2. Passive process.

Active tubular reabsorption is commonly seen with high threshold endogenous substances or nutrients such as electrolytes, glucose, vitamins, amino acids etc. Uric acid is also actively reabsorbed.

- Very few drugs are known to undergo reabsorption actively e.g. oxopurinol.

Passive tubular reabsorption is common for a large number of exogenous substances including drugs. The driving force for such a processes i.e. the concentration gradient is established by the back diffusion or reabsorption of a water along with sodium and other inorganic ions.

- If drug is neither secreted nor reabsorbed, its concentration in the urine will be 100 times that of free drug in plasma due to water reabsorption since less than 1 % of glomerular filtrate is excreted as urine.

Lipophilic drugs are extensively reabsorbed while polar molecules are not. Since a majority of drugs are weak electrolytes, diffusion of such agents through the lipoidal tubular membrane depend upon the degree of ionization which in turn depends on three factors:

1. pH of the urine
2. pKa of the drug
3. Urine flow rate

Urine pH: It is an important factor in the sense that it is not constant like the plasma pH but varies between 4.5 to 7.5. Thus a large pH gradient may exist between urine and plasma.

Thus pH of the urine is dependent upon diet, drug intake and pathophysiology of the patient.

Food rich in carbohydrates results in higher urinary pH whereas proteins lower it. Drugs such as acetazolamide and antacids such as sodium bicarbonate produce alkaline urine while ascorbic acid makes it acidic.

Respiratory and metabolic acidosis and alkalosis result in acidification and alkalinization of the urine respectively.

pKa of the drug: The combined effect of urine pH and drug pKa and lipid solubility on reabsorption of drug is summarized as follows:

1. An acidic drug such as penicillin or a basic drug such as gentamicin which is polar in its unionised form, is reabsorbed passively, irrespective of the extent of ionisation in urine. Excreation of such drugs is independent of pH of urine and flow rate.
2. Very weakly acidic, nonpolar drugs (pKa > 8.0) such as phenytoin or very weakly basic, nonpolar drugs (pKa <6.0) such as propoxyphene are mostly unionised throughout the entire range of urine pH and are therefore extensively reabsorbed passively at all values of urine pH. The rate of excretion of such drugs is always low and insensitive to urine pH.
3. A strongly acidic drugs (pKa $\leq$ 2.0) such as cromoglicic acid or a strongly basic drug (pKa $\geq$ 12.0) such as guanethidine, is completely ionised at all values of urine pH and are, therefore, not reabsorbed. Their rate of excretion is always high and insensitive to pH of urine.
4. Only for an acidic drug in the pKa range 3.0 to 8.0 (e.g. several NSAIDs) and for a basic drug in the pKa range 6.0 to 120 (e.g. morphine analogs, tricyclic antidepressants, etc.) the extent reabsorption is greatly dependent upon urine pH and varies negligible to almost complete.

Urine flow rate: In addition to urine pH and drug pKa, the rate of urine flow also influences the extent of reabsorption. Polar drugs whose excretion is independent of urine pH and are not reabsorbed, are unaffected by urine flow rate.

An increase in urine flow in case of such drugs will only produce more dilute urine. Only those drugs whose reabsorption is pH-sensitive, for example, weak acids and weak bases, show dependence on urine flow rate. For such agents, reabsorption is inversely proportional to the

urinary flow. These compounds can be divided into two types based on their extent of reabsorption in relation to that of water:

1. Drugs which are reabsorbed to an extent equal to or greater than the reabsorption of water eg. Phenobarbital. In such cases, the relationship between renal clearance and urinary excretion is linear.

2. Drugs which are reabsorbed to an extent lower than the reabsorption of water eg. theophylline and many more drugs. In these cases, relationship between renal clearance and urinary excretion is convex curvilinear.

CONCEPT OF CLEARANCE

The clearance concept was first introduced to describe renal excretion of endogenous compounds in order to measure the kidney function. The term is now applied to all organs involved in drug elimination such as liver, lungs, the biliary system, etc. and referred to as hepatic clearance, pulmonary clearance, and biliary clearance and so on.

The sum of individual clearance by all eliminating organs is called as total body clearance or total systemic clearance. It is sometimes expressed as a sum of renal clearance and nonrenal clearance.

Clearance is defined as the hypothetical volume of body fluids containing drug from which the drug is removed cleared completely in a specific period of time. It is expressed in ml/min and is a constant for any given plasma drug concentration.

In comparison to apparent volume of distribution which relates plasma drug concentration to the amount of drug in the body, clearance relates plasma concentration to the rate of drug elimination.

$$\text{Clearance (Cl)} = \frac{Elimination\ rate}{Plasma\ drug\ concentration}$$

Renal Clearance (Cl_R): It can be defined as the volume of blood or plasma which is completely cleared of the unchanged drug by the kidney per unit time. It is expressed mathematically as:

$$Cl_R = \frac{Rate\ of\ urinary\ excretion}{Plasma\ drug\ concentration}$$

Physiologically speaking, renal clearance is the ratio of "sum of rate of glomerular filtration and active secretion minus rate of reabsorption" to "plasma drug concentration C".

$$Cl_R = \frac{Rate\ of\ filtration + Rate\ of\ secretion - Rate\ of\ reabsorption}{Plasma\ drug\ concentration\ (C)}$$

The contribution of each of the above physiological processes in clearing drug cannot be determined by direct measurement. It can however, be determined by comparing the clearance values obtained for a drug with that of an agent such as creatinine or inulin which is cleared by glomerular filtration only. The ratio of these two values is called as renal clearance ratio or excretion ratio.

$$\text{Renal Clearance Ratio} = \frac{Cl_R\ of\ drug}{Cl_R\ of creatinine}$$

Thus, depending upon whether the drug is only filtered, filtered and secreted or filtered and reabsorbed, the clearance ratio will vary. The renal clearance values range from zero to 650 ml/min and the clearance ratio from zero to five.

Factors affecting renal excretion or Renal clearance

Apart from the three physiological processes that govern the urinary excretion, other factors influencing renal clearance of drugs and metabolites are:

1. Physicochemical properties of the drug
2. Plasma concentration of the drug
3. Distribution and binding characteristics of the drug
4. Urine pH
5. Blood flow to the kidneys
6. Biological factors
7. Drug interactions
8. Disease states

Physicochemical properties of the drug

Important physicochemical factors affecting renal excretion of a drug are molecular size, pK, and lipid solubility.

The molecular weight of a drug is very critical in its urinary elimination. An agent of small molecular size can be easily filtered through the glomerulus. Compounds of weights below 300 Daltons, if water-soluble, are readily excreted by the kidneys. Drugs in the molecular weight range 300 to 500 Daltons can be excreted both in urine and bile. Molecules of size greater than 500 Daltons are excreted in urine to a lesser extent.

The influence of drug pKa on excretion has already been discussed. Urinary excretion of an unchanged drug is inversely related to its lipophilicity. This is because, a lipophilic drug is passively reabsorbed to a large extent.

Stereochemical nature of the drug may also influence renal clearance. If a drug exhibits stereoselective protein binding then the drug enantiomers would exhibit differential filtration rates. Active tubular secretion being an active process may also demonstrate stereoselectivity for some drugs.

Indeed, numerous drugs such as chloroquine, disopyramide and terbutaline have been found to be stereoselectively secreted by the kidneys. Active tubular reabsorption also demonstrates these effects as in the case of certain endogenous substances such as glucose and amino acids. Passive reabsorption is unaffected.

Plasma concentration of the drug

Glomerular filtration and reabsorption are directly affected by plasma drug concentration since both are passive processes. A drug that is not Bound to plasma proteins and excreted by filtration only, shows a linear relationship between rate of excretion and plasma drug concentration.

In case of drugs which are secreted or reabsorbed actively, the rate process increases with an increase in plasma concentration to a point when saturation of carrier occurs. With drugs that are actively secreted, the rate of excretion increases with increase in plasma concentration up to a saturation level. After that rate of excretion is decreases.

Distribution and Binding characteristics of the drug

Clearance is inversely related to apparent volume of distribution of drugs. A drug with large V_d is poorly excreted in urine. Drugs restricted to blood compartment have higher excretion rates.

Drugs that are bound to plasma proteins behave as macromolecules and thus cannot be filtered through the glomerulus. Only unbound or free drug appear in the glomerular filtrate. An earlier equation given for renal clearance is:

$$Cl_R = \frac{urine\ drug\ concentration}{Plasma\ drug\ concentration}\ Urine\ flow\ rate \ldots\ldots\ldots\ldots\ldots\ldots(1)$$

Since only free drug can be excreted in the urine, the fraction of drug bound to plasma proteins is important and can be computed from equation:

$$f_u = \frac{C_u}{C} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2)$$

Where, f_u = fraction of unbound drug in plasma
C_u = concentration of unbound drug in plasma
C = total plasma concentration of drug

Thus, equation can be written as:

$$\mathbf{Cl_R = f_u \,.\, Urine\ flow\ rate}$$

Drugs extensively bound to proteins have long half-lives because the renal clearance is small and urine flow rate is just 1 to 2 ml/min. The renal clearance of oxytetracycline which is 66 % unbound is 99 ml/min while that of doxycycline (7% bound) is just 16 ml/min.

Actively secreted drugs are much less affected by protein binding, e.g. penicillins. The free fraction of such drugs are filtered as well as secreted actively and dissociation of drug protein-complex occurs rapidly.

Blood flow to the kidneys

The renal blood flow is important in case of drugs excreted by glomerular filtration only and those that are actively secreted. In the secretion, increased perfusion increases the contact of drug with the secretary sites and enhances their elimination. Renal clearance in such instances is said to be perfusion rate-limited.

Biological Factors

Age, sex, species and strain differences, differences in the genetic make-up, circadian rhythm, etc. alter drug excretion. Renal excretion is approximately 10% lower in females than in males. The renal function of newborns is 30 to 40% less in comparison to adults and attains maturity between 2.5 to 5 months of age. In old age, the GFR is reduced and tubular function is altered, the excretion of drugs is thus slowed down and half-life is prolonged.

Drug Interactions

Any drug interaction that results in alteration of protein-drug binding characteristics, renal blood flow, active secretion, urine pH and intrinsic clearance and forced diuresis would alter renal clearance of a drug.

- ***Alteration in P-D binding:*** The renal clearance of a drug extensively bound to plasma proteins is increased after displacement with another drug. An interesting example of this is gentamicin induced nephrotoxicity by furosemide. Furosemide does not precipitate this effect by its diuretic effect but by displacing gentamicin from binding sites. The increased free antibiotic concentration accelerates its renal clearance.
- ***Alteration of urine pH:*** Acidification of urine with ammonium chloride, methionine or ascorbic acid enhances excretion of basic drugs. Alkalinization of urine with citrates, tartarates, bicarbonates and carbonic anhydrase inhibitors promote excretion of acidic drug.
- ***Competition for active secretion:*** Phenylbutazone competes with hydroxy hexamide, the active metabolite of antidiabetic agent acetohexamide, for active secretion and thus prolongs its action.
    - Probenecid is a competitive inhibitor of organic anion transport system
    - Cimetidine is competitive inhibitor of organic cation transport system
- ***Forced Diuresis:*** All diuretics increase elimination of drugs whose renal clearance gets affected by urine flow rate.

Disease States-Renal Impairment

Renal dysfunction greatly impairs the elimination of drugs especially those that are primarily excreted by the kidneys.

Some of the causes of renal failure are hypertension, diabetes mellitus, hypovolemia (decreased blood supply to the kidneys), pyelonephritis (inflammation of kidney due to infections, etc.), and aeroallergens (e.g. nephrotoxic serum) and nephrotoxic agents such as aminoglycosides. phenacetin and heavy metals such as lead and mercury.

Uremia, characterized by impaired glomerular filtration and accumulation of fluids and protein metabolites, also impairs renal clearance of drugs.

In both these conditions, the half-lives of drugs are increased. As a consequence, drug accumulation and toxicity may result. Determination of renal function is therefore important in such conditions in order to monitor the dosage regimen.

RENAL FUNCTION AND RENAL FAILURE

Renal function can be determined by measuring the GFR. Both endogenous and exogenous substances have been used as markers to measure GFR.

In order to be useful as a marker the agent should entirely get excreted in unchanged form by glomerular filtration only and should be physiologically and pharmacologically inert.

The rate at which these markers are excreted in urine reflects the GFR and change in GFR reflects renal dysfunction. **Inulin** (the exogenous fructose polysaccharide) and **serum creatinine level** have been used successfully for such purposes.

Inulin clearance provides an accurate measure of GFR but has the disadvantage of being a tedious method. Clinically, creatinine clearance is widely used to assess renal function.

Creatinine is an endogenous amine produced as a result of muscle catabolism. It is excreted unchanged in the urine by glomerular filtration only.

An advantage of this test is that it can be correlated to the steady state concentration of creatinine in plasma and needs no collection of urine. The method involves determination of serum creatinine levels. Since, creatinine production varies with age, weight and gender, different formulae are used to calculate creatinine clearance from the serum creatinine values.

A direct method for determining creatinine clearance is determination of the amount of creatinine excreted in urine in 24 hours (to calculate the rate of creatinine excretion) and the mean of serum creatinine from blood samples taken just before and immediately after the urine collection period. Following formula is used:

$$\mathbf{Cl_R} = \frac{\boldsymbol{Rate\ of creatinine\ excretion}}{\boldsymbol{serum\ creatinine\ in\ mg}\ \%}$$

The normal creatinine clearance value is 120 to 130 ml/min. A value of 20 to 50 ml/min denotes moderate renal failure and values below 10 ml/min indicate severe renal impairment.

The renal function, RF is calculated by following equation

$$\mathbf{RF} = \frac{\boldsymbol{Cl_{cr}\ of\ patient}}{\boldsymbol{Cl_{cr}\ of\ a\ normal\ person}}$$

Dose Adjustment in Renal Failure

Generally speaking, drugs in patients with renal impairment have altered pharmacokinetic profile. Their renal clearance and elimination rate are reduced, the elimination half-life is increased and the apparent volume of distribution is altered. Thus, dose must be altered depending upon the renal function in such patients.

However, except for drugs having low therapeutic indices, the therapeutic range of others is sufficiently large and dosage adjustment is not essential.

Dosage regimen need not be changed when

- The fraction of drug excreted unchanged, f_u is ≤ 0.3. and
- The renal function RF is ≥ 0.7 of normal.

The above generalization is based on the assumption that the metabolites are inactive and binding characteristics and drug availability are unaltered and so is the renal function in kidney failure conditions.

When the f_u value approaches unity and RF approaches zero, elimination is extremely slowed down and dosing should be reduced drastically. The significance of nonrenal clearance increases in such conditions.

The required dose in patients with renal impairment can be calculated by the simple formula:

Drug dose in renal impairment = Normal dose × RF

The dosing interval in hours can be computed from the following equation:

$$\textbf{Dosing interval} = \frac{\textit{Normal interval in hours}}{RF}$$

When the drug is eliminated both by renal and nonrenal mechanisms the dose to be administered in patients with renal failure is obtained from following equation.

Drug Dose = Normal dose [RF × Fraction excreted in urine + Fraction eliminated normally]

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