# PHARMACOLOGY

## Excretion of Drugs

Objectives:

- Identify main and minor routes of Excretion including renal elimination and biliary excretion
- Describe enterohepatic circulation and its consequences on duration of drugs.
- Describe some pharmacokinetics terms including clearance of drugs.
- Biological half-life (t ½), multiple dosing, steady state levels, maintenance dose and Loading dose.

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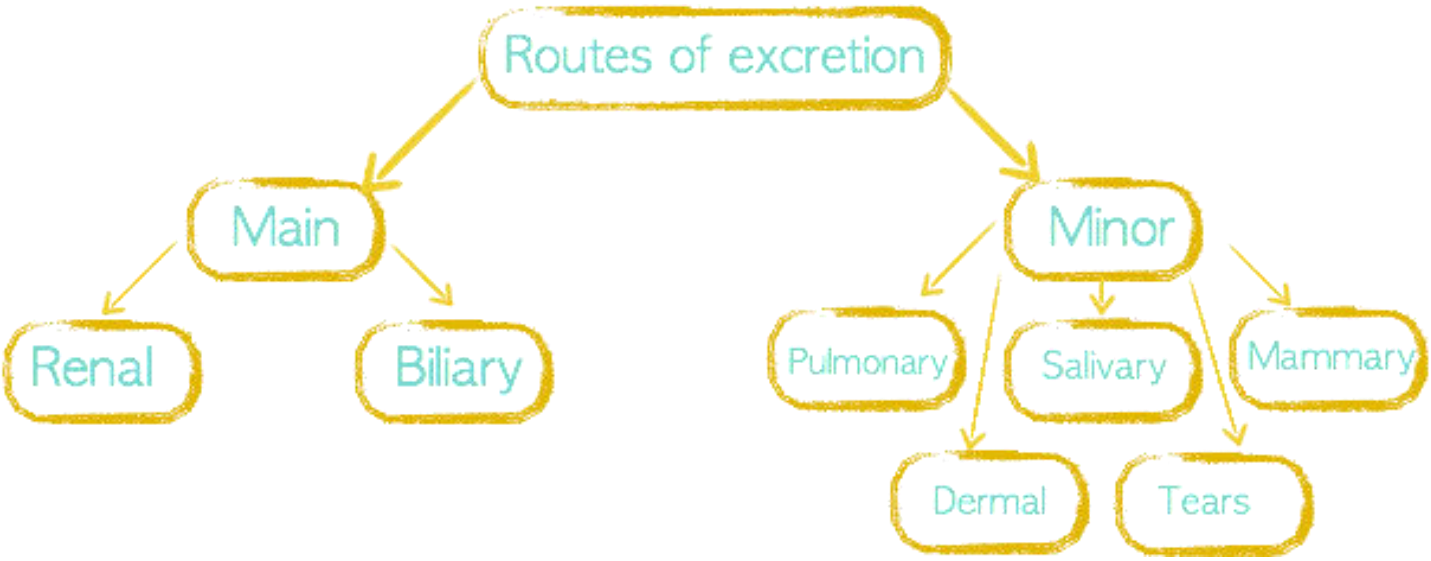
# Excretion:




**Nephron**( the structure unit of kidney )**consist of:**

- Glomerulus Proximal convoluted tubules
- Loop of Henle
- Distal convoluted tubules
- Collecting ducts

## The principle processes that determine the Urinary excretions of drugs are:

### Glomerular filtration (GFR):

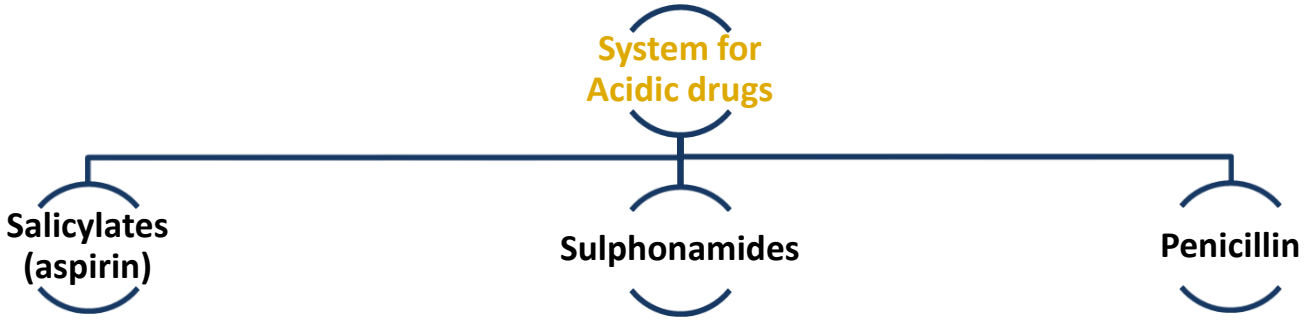
- Depends upon renal blood flow (600 ml/min)
- GFR 20% of renal blood flow = 125 ml/min.
- Glomerular filtration occurs to low molecular weight drugs
- Only free drugs (unbound to plasma proteins) are filtered

### Active tubular secretion:

- occurs mainly in proximal tubules; increases drug concentration in lumen
- organic anionic and cationic transporters mediate active secretion of anionic and cationic drugs.
- can transport drugs against conc. gradients.
- e.g. **Penicillin**

### Passive tubular re-absorption

- In distal convoluted tubules & collecting ducts.
- Passive diffusion of unionized, lipophilic drugs
- Lipophilic drugs can be reabsorbed back into blood circulation and excretion in urine will be low.
- Ionized drugs are poorly reabsorbed so urinary excretion will be high.




Transport of acidic drugs is blocked by probenecid (It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing serum urate levels).


The suffix -ine means that the drug is coming from natural sources (glands) and it is basic

## Urinary pH trapping (Ion trapping)

- Changing pH of urine by chemicals can inhibit or enhance the drug reabsorption from renal tubules back into blood circulation.
- Ion trapping is used to enhance renal clearance of drugs during toxicity.
- Urine is slightly acidic and favors excretion of basic drugs.
- Acidification of urine using **ammonium chloride (NH4Cl)** increases excretion of basic drugs as **amphetamine**.
- Alkalization of urine using **sodium bicarbonate ($NaHCO_3$)** increases excretion of acidic drugs as **aspirin**.

# Major Routes of Excretion

## Renal Excretion

Drugs excreted mainly by the kidney include:

- Aminoglycosides antibiotics (as gentamycin)
- Penicillin
- Lithium

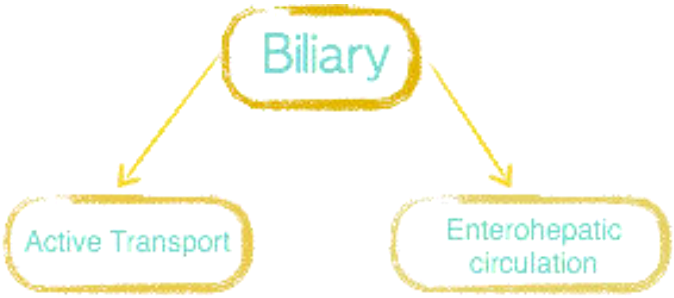
These drugs should be prescribed carefully in:

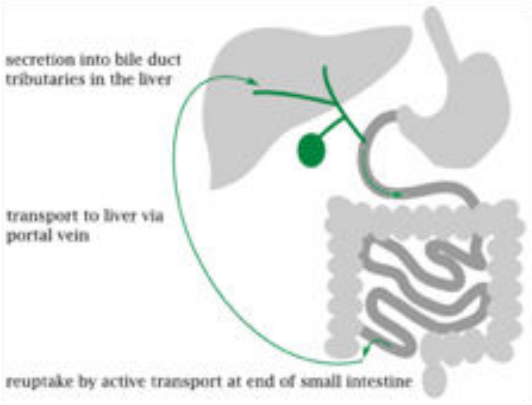
- Patients with renal disease
- Elderly people

## Biliary Excretion

- Occurs to few drugs that are excreted into feces.
- Such drugs are secreted from the liver into bile by active transporters, then into duodenum.

Some drugs undergo enterohepatic circulation back into systemic blood circulation.




- Drugs excreted in the bile in the form of glucouronides will be hydrolyzed in intestine by bacterial flora liberating free drugs that can be reabsorbed back into blood if the drugs are lipid soluble.
- This prolongs the duration of action.

**How?**
Glucourinase enzyme breaks down the glucouronide conjugate into (drug+gluronic acid) then the drug (if lipid-soluble) will be reabsorbed by the intestines

Examples: digoxin, thyroxine and morphine.

## Short ($t_{1/2}$)

Examples:

- Penicillin.
- Tubocurarine.

## Long ($t_{1/2}$)

Examples:

- Digoxin.(treats heart failure)
- Thyroxine.

**Plasma half-life ($t_{1/2}$)** is the time required for the plasma concentration of a drug to fall to half of its initial concentration (a measure of duration of action).

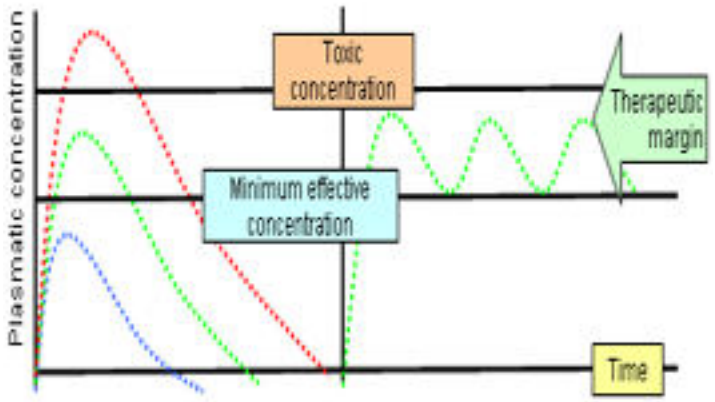
Determines the dosing interval

Factors that may increase half-life

- Decreased metabolism
  - -Liver disease.
  - -Microsomal inhibitors. ex: grapefruit
- Decreased clearance
  - -Renal disease.
  - -Congestive heart failure.
- High binding of drugs
  - -Plasma proteins.
  - -Tissue binding.
- Enterohepatic recycling

# Steady State level:

A state at which the therapeutic plasma concentration of the drug (mg/ml) remains constant with the therapeutic window (the range between effective and toxic levels of drugs).
rate of drug administration = elimination rate




Not toxic and yet, effective

**Therapeutic window:**

The range at which the state of the drug is steady, (drug in= drug out) without reaching toxicity level

3-5 half lives would be necessary to reach the steady state concentration.
E.g. Morphine

# Loading dose:

is the initial dose that is given to achieve rapid therapeutic plasma level.

- After administration of the drug, the plasma concentration decreases due to distribution of drug to other tissues
- These doses balance the drug distribution
- This is important for drugs with long half lives
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## Clinical application for the loading dose:

- A loading dose may be desirable if the time required to attain steady state of drug (4 elimination t1/2 values) is long and rapid relief is required in the condition being treated.
- E.g. t1/2 of Lidocaine (antiarrhymthic drug) is usually 1-2 hours and Arrhythmias after myocardial infarction are life-threatening. One cannot wait 4-8 hours to achieve a therapeutic concentration.
- So we use a loading dose of Lidocaine in the coronary care unit.

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# Maintenance doses:

- Are the doses required to maintain the therapeutic level of the drug constant or the steady state of the drug.
- - These doses balance the amount of drug lost during metabolism and clearance.
- - The patient needs to take regular doses of a drug such as Amoxicillin (500 mg) / 8 hours to maintain the therapeutic level

# THANK YOU FOR CHECKING OUR WORK

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