PHARMACOLOGY
TEAM 439

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MED439
KING SAUD UNIVERSITY

# Excretion of Drugs

If you didn't understand any part from this lecture Click here!

- Important
- In male and female slides
- Only in male slides
- Only in female slides
- Extra information

# Objectives

- Identify the main and minor routes of excretion including renal elimination and biliary excretion.
- Describe the enterohepatic circulation and its consequences on

  duration of actions of drugs.

- Describe pharmacokinetics terms including clearance of drugs, half-life (t 1/2), steady state levels, maintenance dose and loading dose.

Any Future corrections will be posted on the editing file.
make sure to check it **frequently**

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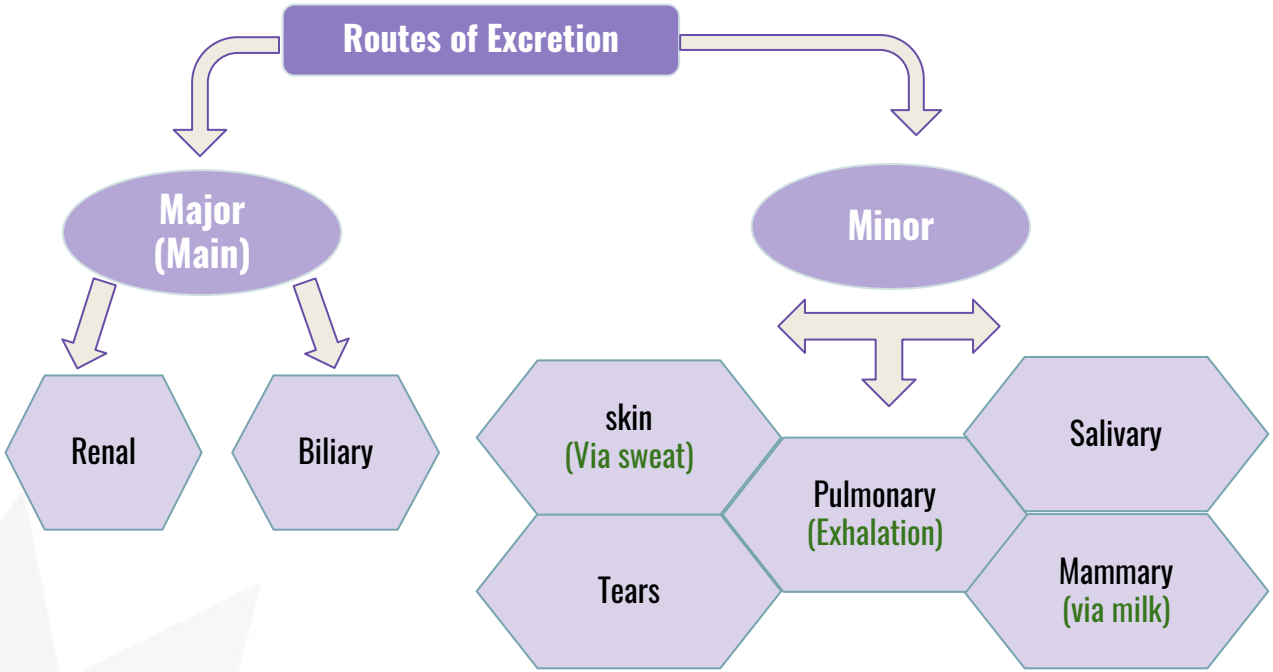



**Structure of kidney :**

The structure unit of kidney is **nephron**, that consists of :

1. Glomerulus .
2. Proximal convoluted tubules.
3. Loop of Henle .
4. Distal convoluted tubules.
5. Collecting ducts.

The principle processes that determine the urinary excretion of drugs are:

**Renal Excretion= Filtration* – Reabsorption** + Secretion*****

*Glomerular filtration.

**Passive tubular reabsorption.

*** Active tubular secretion.

# The principle process that determine the urinary excretion of drugs

**Glomerular Filtration Rate (GFR).**

1- Depends upon renal blood flow (600 ml/min)
2- GFR 20% of renal blood flow = 125 ml/min.
3- Glomerular filtration occurs to:
- free drugs (unbound to plasma proteins).
- Low molecular weight drugs.

**Passive Tubular Reabsorption.**

1-In distal convoluted tubules & collecting ducts.
2-Passive diffusion of **unionized, lipophilic** drugs.
3- Lipophilic drugs can be **reabsorbed back into blood** circulation and excretion in urine will be low. ( لأنه رجع للدم فبيكون قليل ).
4-Ionized drugs are poorly reabsorbed & so urinary excretion will be high.

**Active Tubular Secretion.**

1-occurs mainly in **proximal tubules**; increases drug concentration in tubular lumen.
2- organic **anionic** and **cationic** transporters mediate active secretion of **anionic** and **cationic** drugs.
3- can transport drugs against conc. gradients.
E.g: Penicillin is an actively secreted drug

Active tubular secretion has **two systems** One for **acidic drugs** and the other for **basic drugs**

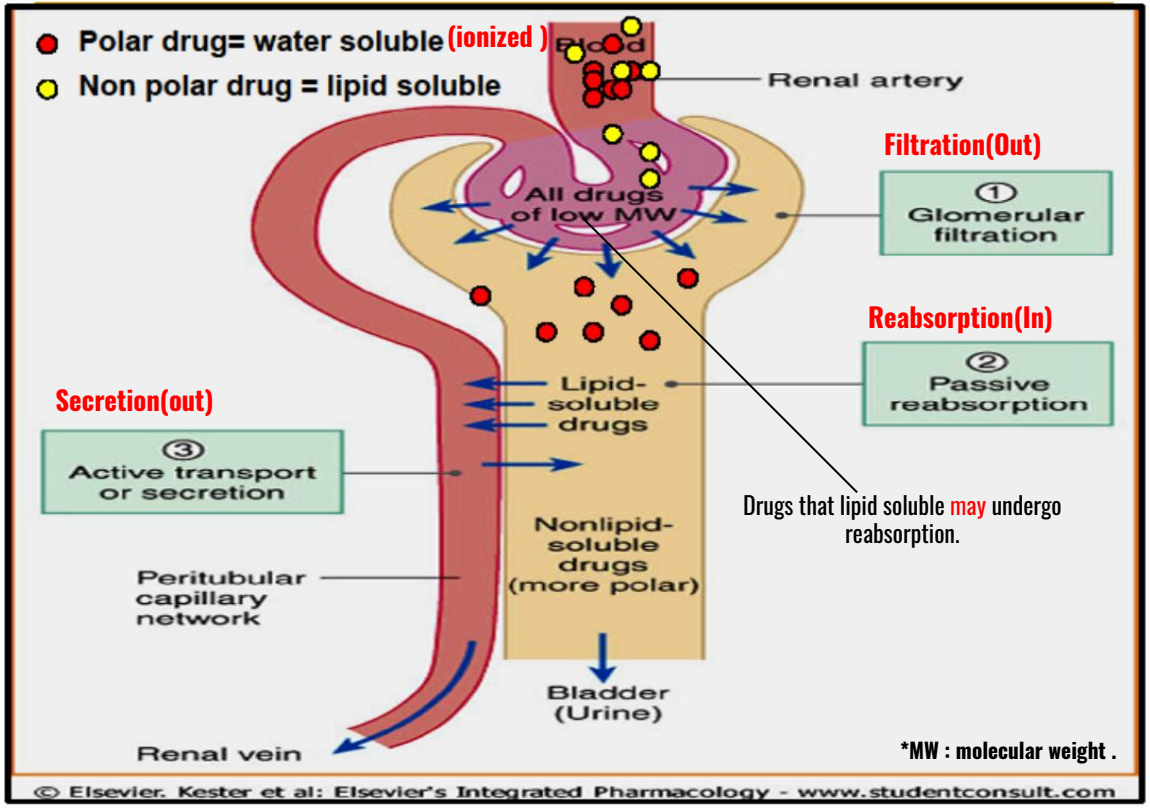
**Acidic drugs:**

1- Salicylates (aspirin)
2- sulphonamides
3- Penicillin
Transport of acidic drugs is blocked by **probenecid**

**Basic drugs:**

1- Morph**ine**
2- Atrop**ine**
3- quin**ine**
4- neostigm**ine**
the suffix "**ine**" means that the drug is basic

# Renal Excretion (Total Out) = Filtration(Out) - Reabsorption(in) + Secretion(out)




the reabsorption is a negative value in the equation because renal excretion measures the **OUT**put

# Urinary pH trapping (Ion trapping)

Changing of P(H) urine by chemicals can either **enhance** or **inhibit** the renal excretion of drugs

Urine is normally **slightly acidic** and favors Excretion of **Basic drugs**

**Acidification** Of urine
By ammonium chloride **(NH4CL)**

Excretion of **Basic drugs**

Ex:amphetamine

**Alkalinization** of urine
By sodium bicarbonate (NaHCO3)

excretion of **acidic drugs**

Ex:aspirin

Ion tapping is used to enhance renal clearance of drugs **during toxicity**

# Main routes of excretion

## Renal Excretion

Drugs excreted <u>mainly</u> by the kidney
1-Aminoglycosides antibiotics (as gentamycin)
2-B-lactam antibiotics as penicillin
3-Lithium

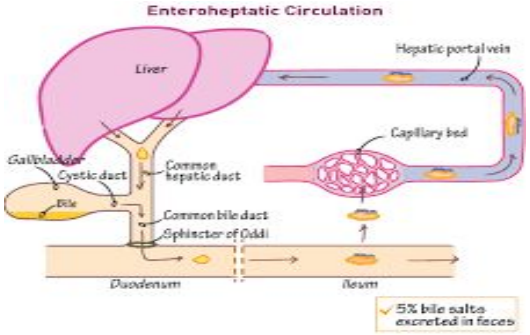
*Drugs should prescribe carefully for:
1-patients with renal disease.
2-Elderly people

*Because their kidney functions may be **low** or **damaged**

## Biliary Excretion

(Occurs to few drugs that are **excreted into feces**)
It has two types:

1) drugs are secreted from the liver into bile by **active transporters** into **duodenum**.




2) Some drugs undergo **Enterohepatic circulation***

(where they move back through the hepatic portal vein towards the liver and then **back to the systemic circulation**)

-Drugs excreted in the bile in the form of **glucuronides** **Will hydrolyze in intestine by bacterial flora** liberating free drugs which can be reabsorbed back into blood **if the drugs are lipophilic**

**This prolongs the duration of action of drugs**

Ex: digoxin, thyroxine and morphine

# Plasma Half-life (t1/2)

Is time required for the plasma concentration of a drug to fall to ½ of its initial concentration.

**a measure of duration of action.**

Determine the dosing interval

Drugs of long plasma half life

Digoxin, Thyroxine

Drugs of short plasma half life

Penicillin G, tubocurarine.

Muscle relaxant

*Plasma in blood

## Factors May Increase Plasma half-life (t ½)

- Enterohepatic recycling
- Decreasing metabolism
  - Liver disease
  - Microsomal inhibitors
- Decreasing clearance
  - Renal disease
  - Congestive heart failure
- High binding of drugs
  - Plasma proteins
  - Tissue binding

*Decreased metabolism depends on enzymes
*Liver disease are also called hepatic disorder

# Steady state

**A state at which the therapeutic plasma concentration of the drug (mg/ml) remains constant with the therapeutic window**

Therapeutic window:

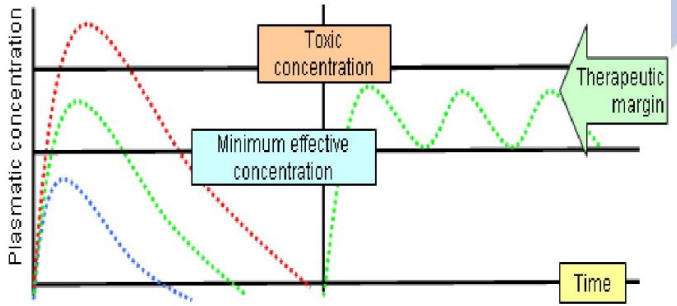
the range between the effective & toxic level of the drug

Steady state concentration is attained after 3-5 half lives

At steady state : the amount of drug eliminated equals the amount of drug administered

Rate of drug administration = Rate of drug Elimination

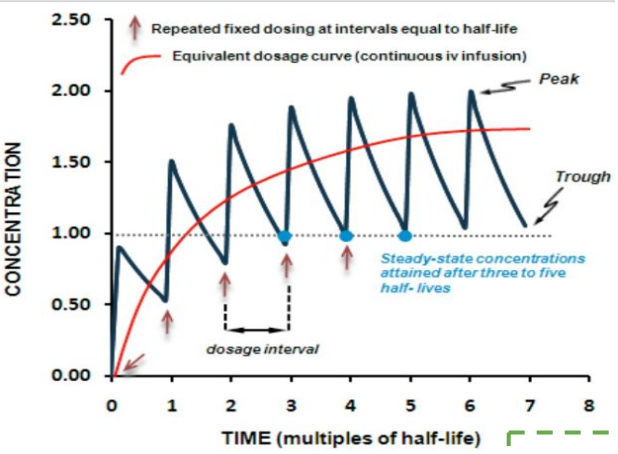
*What remains is the therapeutic dose




t1/2 can be used to predict how long it will take from the start of dosing to reach steady-state levels during multiple dosing

to calculate: add 100 every t1/2 and then divide by 2

| No. of t1/2 | Concentration achieved (% of steady conc) |
|---|---|
| 0 | 100% |
| 1 | 50% |
| 2 | (50+100) 75% |
| 3 | (75+100) 87.5% |
| 4 | (87.5+100) 94% |
| 5 | (94+100) 97% |




helps to understand

## Loading Dose

Is the **large** **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 balances the drug distribution.

**This is important for drugs with long half lives.**

Loading doses= Vd x required plasma drug concentration

## Clinical Application of 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. lidocaine (antiarrhythmic drug) with t1/2 of around 1-2 hours.
E.g. Arrhythmias after myocardial infarction are life-threatening, and one cannot wait several hours (4-8 hours) to achieve a therapeutic concentration.

steady state= 3-5 X 2 hour= 6-10 hours

**Use of a loading dose of lidocaine in the coronary care unit is standard.**

## Maintenance Doses

Are the doses required to maintain the therapeutic level of the drug constant or the steady state of the drug.

The patient needs to take regular doses of a drug such as amoxicillin (500 mg) / 8 hours to maintain the therapeutic level.

These doses balance the amount of drug lost during metabolism and clearance.

Maintenance dose= clearance x required plasma concentration

## Summary

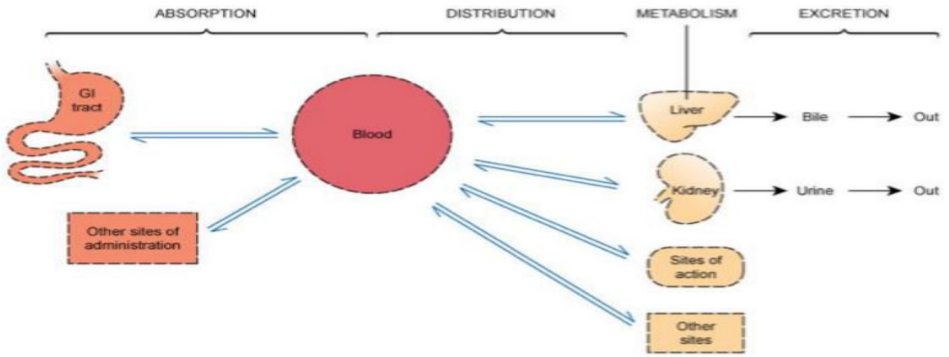
Polar drugs are readily excreted and poorly reabsorbed.

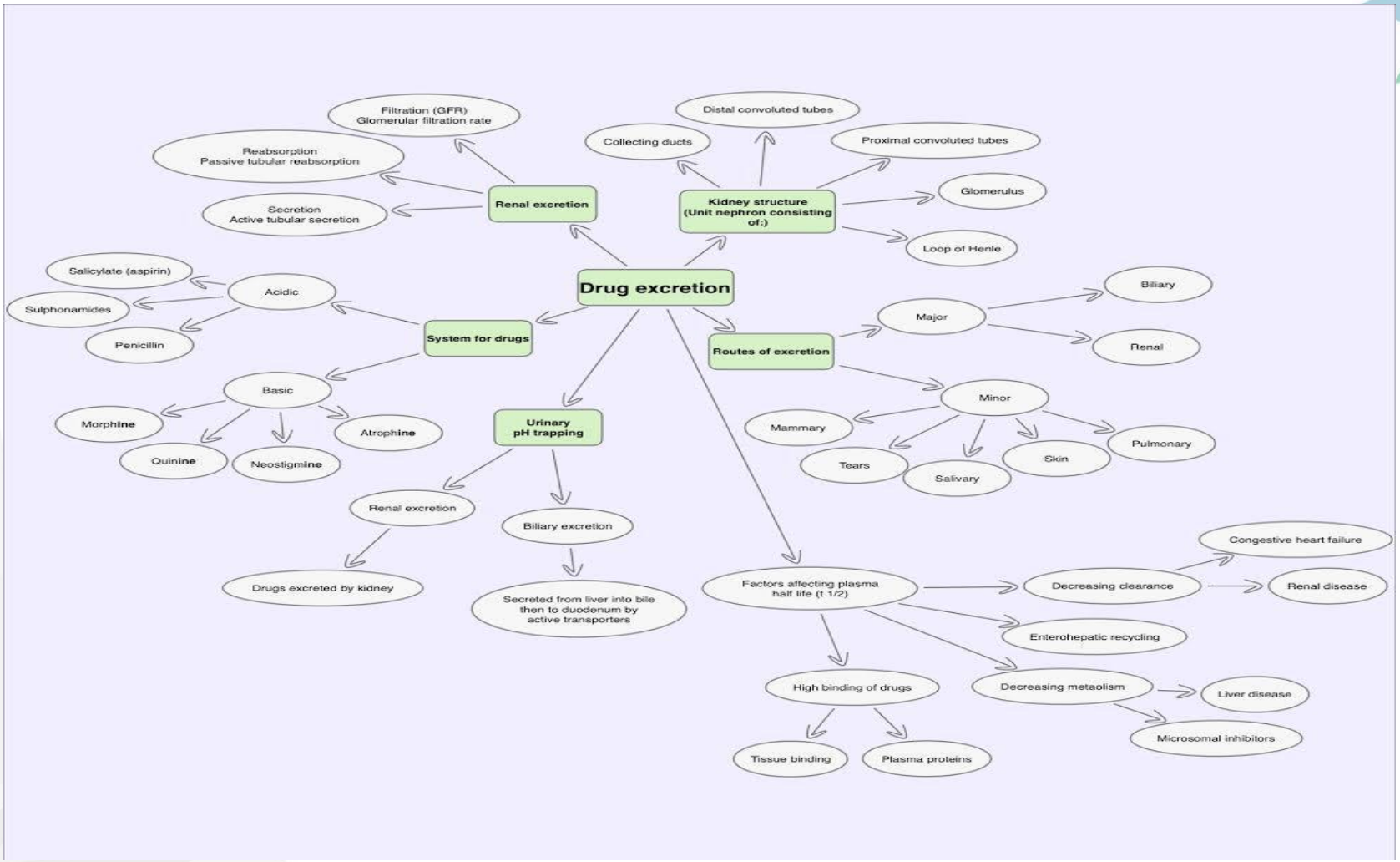
Lipid soluble drugs are reabsorbed back and excretion will be low

Acidic drugs are best absorption in (acidic medium ) best excreted in alkaline urine (sodium bicarbonate).

Basic drugs are best absorption in (basic medium ) , best excreted in acidic urine (ammonium chloride)..

Enterohepatic circulation prolongs half life of the drug.




Drug excretion
Renal excretion
Filtration (GFR)
Glomerular filtration rate
Reabsorption
Passive tubular reabsorption
Secretion
Active tubular secretion
Kidney structure
(Unit nephron consisting of:)
Distal convoluted tubes
Collecting ducts
Proximal convoluted tubes
Glomerulus
Loop of Henle
System for drugs
Acidic
Salicylate (aspirin)
Sulphonamides
Penicillin
Basic
Morphine
Quinine
Neostigmine
Atrophine
Urinary
pH trapping
Renal excretion
Drugs excreted by kidney
Biliary excretion
Secreted from liver into bile then to duodenum by active transporters
Routes of excretion
Major
Biliary
Renal
Minor
Mammary
Tears
Salivary
Skin
Pulmonary
Factors affecting plasma half life (t 1/2)
Decreasing clearance
Congestive heart failure
Renal disease
Enterohepatic recycling
High binding of drugs
Tissue binding
Plasma proteins
Decreasing metaolism
Liver disease
Microsomal inhibitors

# MCQ

| 1)Glomerular filtration occurs to: | | | |
|---|---|---|---|
| A- low MW Drugs | B- high MW Drugs | C- bounded Drugs (to plasma protein) | D- all the Drugs |

| 2) An example of acidic drugs: | | | |
|---|---|---|---|
| A- morphine | B- penicillin | C- quinine | D- atropine |

| 3) GFR is about ..... of renal blood flow | | | |
|---|---|---|---|
| A- 3-5% | B-20% | C-30% | D- 50% |

| 4) Active tubular secretion occurs mainly in : | | | |
|---|---|---|---|
| A- Glomerulus | B- Loop of Henle | C- Collecting ducts | D- proximal tubules |

| 5) Which factor that may decrease half life (½ t ): | | | |
|---|---|---|---|
| A- decreased metabolism | B- high binding of drugs | C- low binding of drugs | D- enterohepatic recycling |

## ANSWERS

| | |
|---|---|
| 1 | A |
| 2 | B |
| 3 | B |
| 4 | D |
| 5 | C |

# SAQ

1) What is the plasma half-time?

2) The range between the effective and toxic level of the drug called?

3) What can we use to have better excretion of penicillin through ion trapping?

4) Give an example for a drug with a short half life and a drug with a long half life.

## ANSWERS

A1) ~~It's the time which required for the plasma concentration of drug to fall to half of its initial concentration~~

A2) ~~Therapeutic window~~

A3 ~~Sodium BiCarbonate [NaHCO3]~~

A4) ~~**Penicillin G** has a short life time and **Digoxin** has a long half life~~

# GOOD LUCK!

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