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MED444
KING SAUD UNIVERSITY

PHARMACOLOGY
TEAM 444

Drug Excretion

Lecture no. 4

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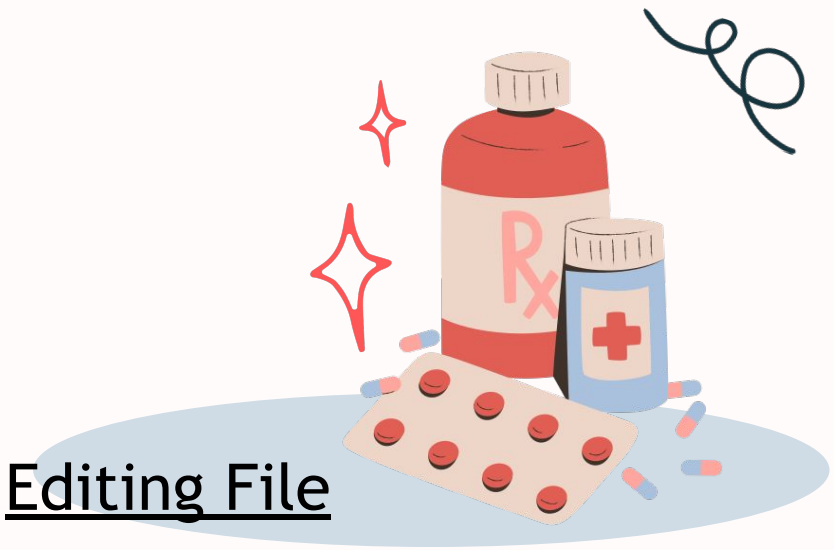

Editing File

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Objectives

- **Identify major 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 some pharmacokinetics terms including clearance of drugs, biological half-life (t ½), multiple dosing, steady state levels, maintenance dose and loading dose.**

helpful videos:

Routes of excretion

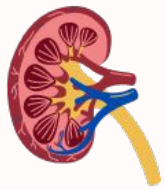
Absorption → Distribution → Metabolism → **Excretion**

Routes of Excretion

- **Main**
  - Renal Excretion urine
  - Biliary Excretion feces
- **Minor**
  - Pulmonary Excretion (Exhalation)
  - Salivary Excretion.
  - Mammary Excretion via milk
  - Skin / Dermal Excretion via sweat
  - Tears

Renal Excretion

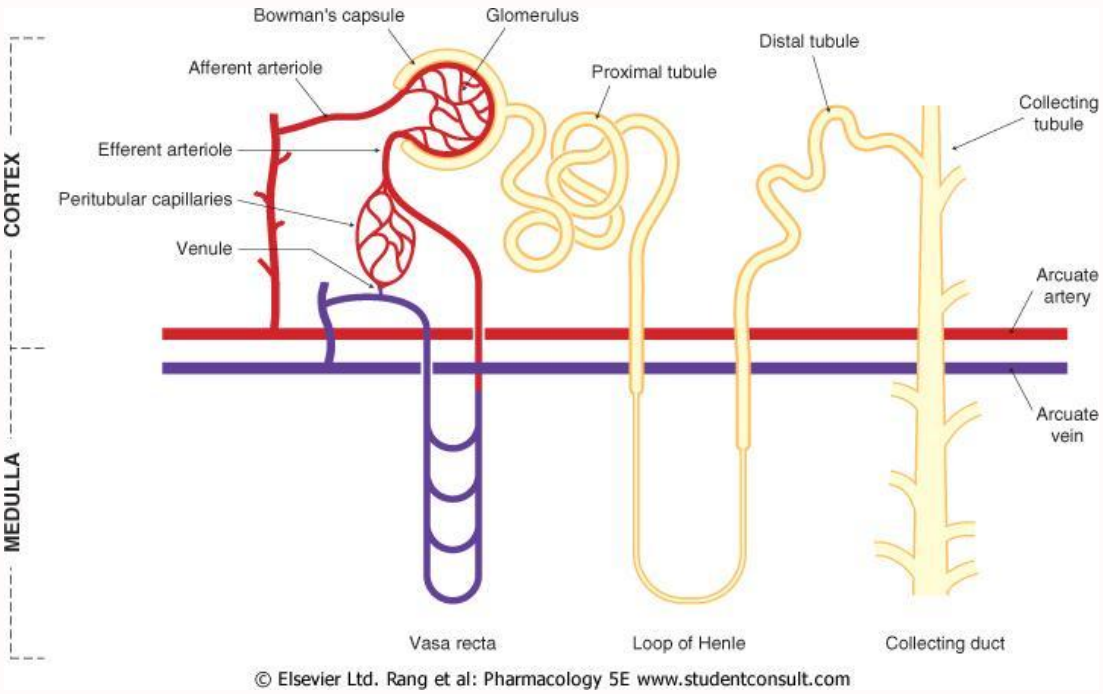
Structure of kidney



The structure unit of kidney is nephron.
That consists of :

- Glomerulus (filtration)
- Proximal convoluted (secretion) tubules
- Loop of Henle
- Distal convoluted tubules
- Collecting ducts

Kidney anatomy



Renal Excretion includes:

The principal processes that determine the urinary excretion of drugs are:
Renal Excretion= Filtration – Reabsorption + Secretion

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Glomerulus
-collection of blood vessels
-The site of filtration
-if the drug low+free it will be filtered and will continue moving
-it will be called filtrate

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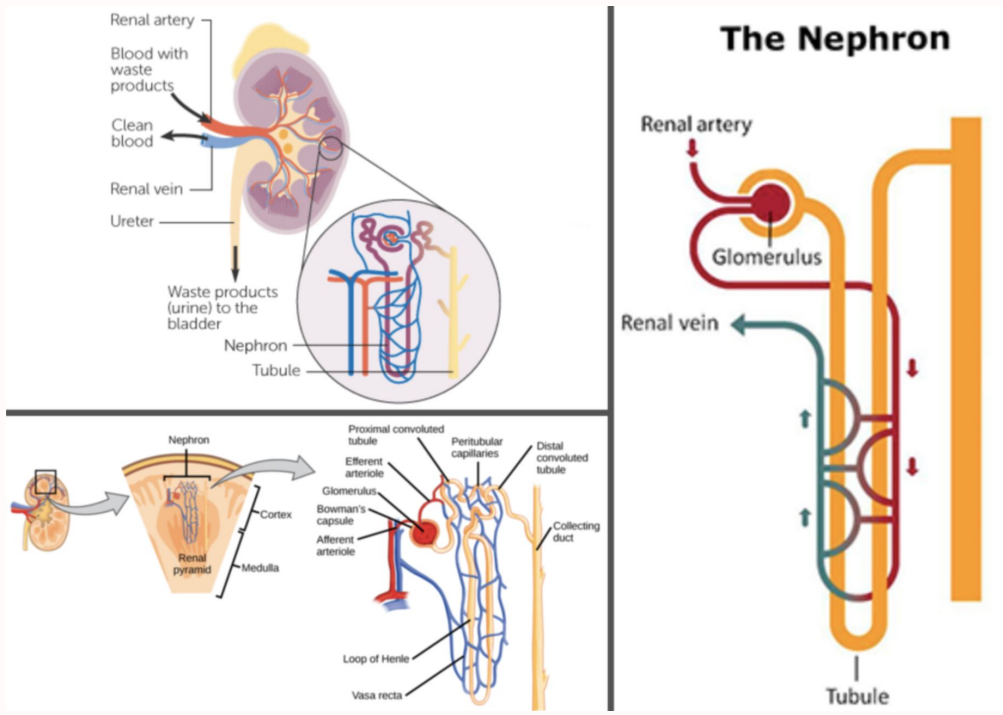
Two things will happen after filtration (adding-removing)
1-adding by tubular secretion
2-when it reaches its final result (urine)



This picture from males' slide

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Dr. Note:
*Glucose urea if it's high it means there are problems in the kidney function because normally even if the glucose goes filtration it will be reabsorption

** glucose and protein urea are NOT normal

Renal Excretion Includes

The principle process that determine urinary excretion of drugs

1- 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 while bound drugs are not filtered.

more blood flow ⟹ more filtration

probenecid
- high affinity
- competitive drug
- acidic drug

drug-drug interaction
- Probenecid bind to the carrier
- penicillin reabsorbed
- resulting in long duration for penicillin

2- Active tubular secretion.

Dr. Note
All drugs in Active tubular secretion to get out of the kidney need ?
1. ATP molecule 2. Carrier

- occurs mainly in proximal tubules; increases drug concentration in tubular lumen.
- Organic anionic and cationic transporters mediate active secretion of anionic and cationic drugs. (specific-selective carrier-can be saturated)
- Can transport drugs against conc. gradients Need ATP
- E.g Penicillin is an example of actively secrete drug.

Transporters for acidic drugs:

System for Acidic drugs.
- Salicylates (aspirin)
- Sulphonamides
- Penicillin (antibiotic)

(Transport of acidic drugs is blocked by probenecid)

(used to slow down the rate of excretion so it will prolong duration-less frequency)

Transporters for basic drugs:

System for Basic drugs
- Morphine
- Atropine
- Quinine
- Neostigmine

the suffix "ine" means that the drug is basic

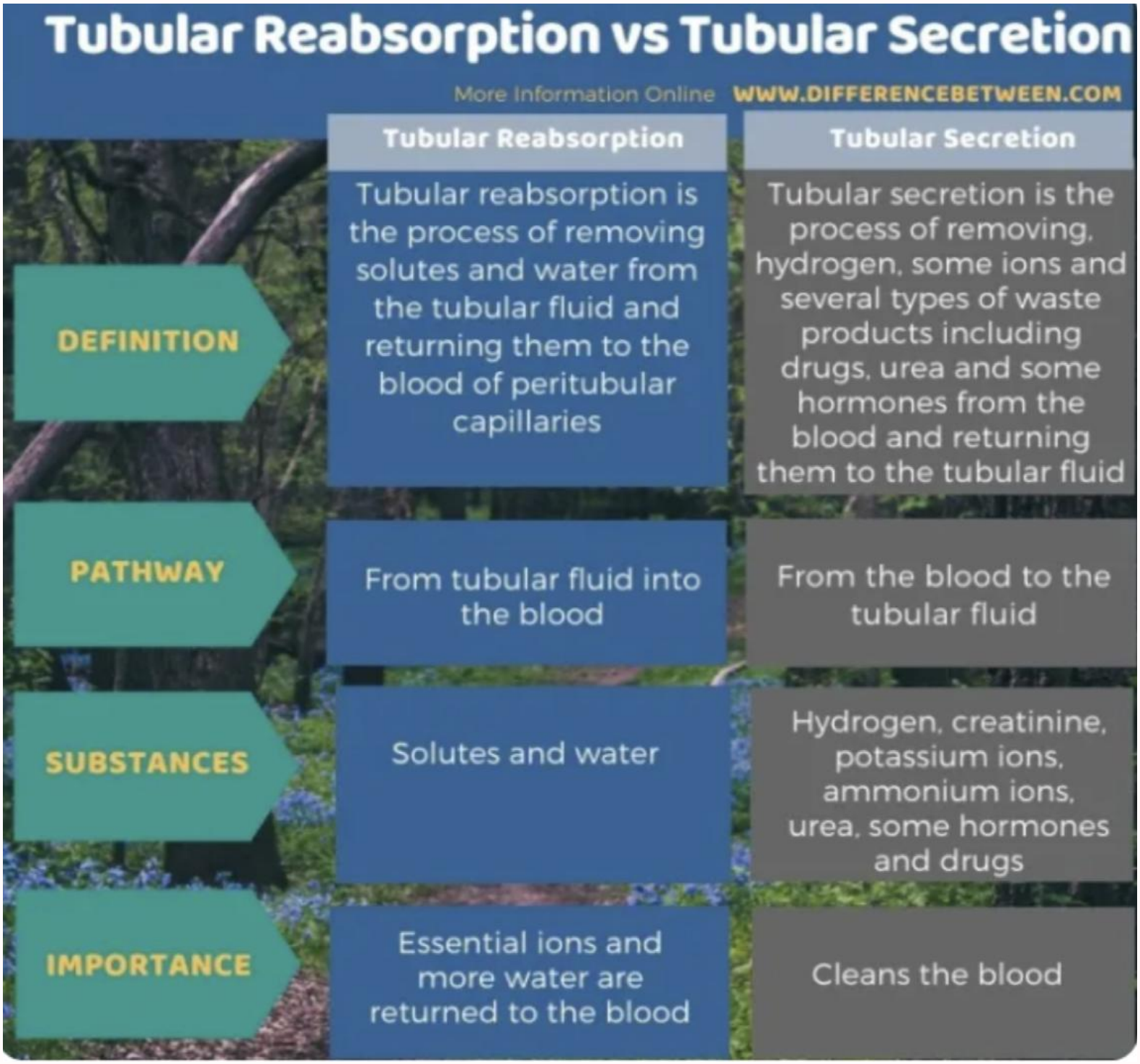
Dr. Note: Basic drugs:
1.Natural source
2.Lipid soluble
3.Act centrally
4.Good absorption
5.Large volume of distribution Acidic is the opposite

3- Passive tubular reabsorption:
if it isn't water soluble

- In distal convoluted tubules & collecting ducts
- Passive diffusion of unionized, lipophilic drugs
- Lipophilic drugs can be reabsorbed back from tubular lumen to blood circulation and **Excretion** in urine will be low. (لانه رجع للدم)
- Ionized drugs are poorly reabsorbed & so urinary excretion will be high (because it's water soluble)

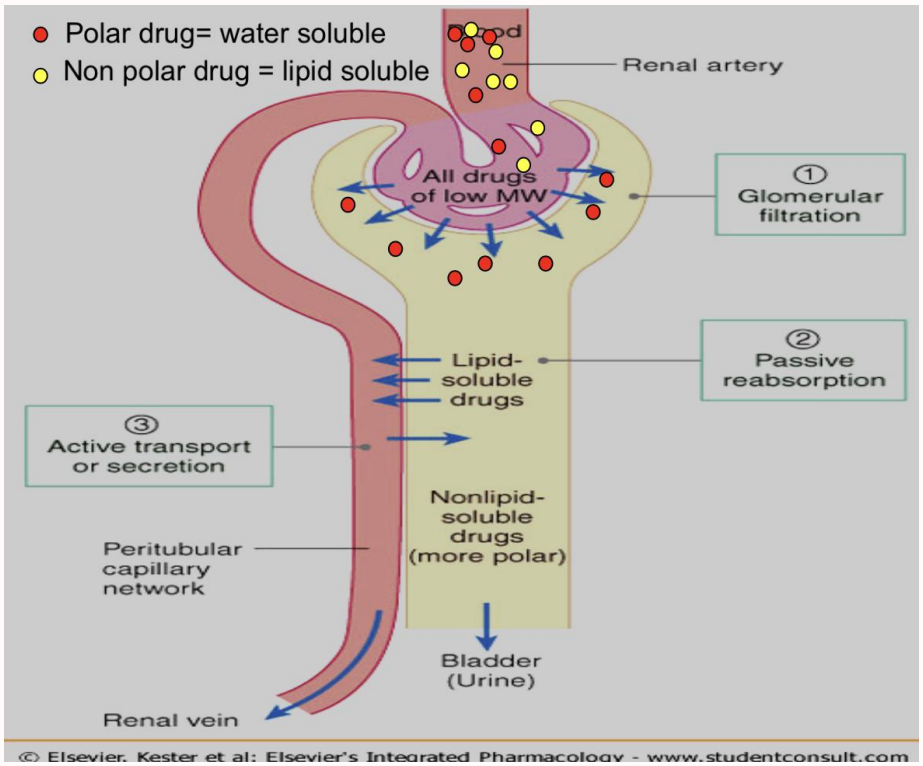
tubular reabsorption vs secretion

This picture from males' slide

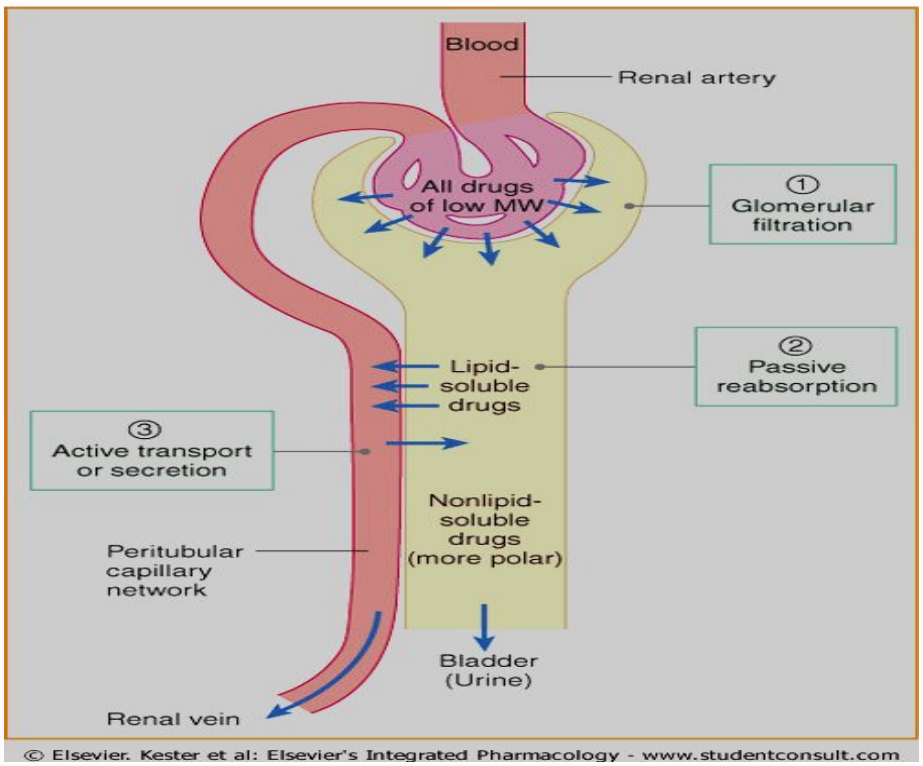


Renal Excretion Includes

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



#med439
the reabsorption is a negative value in the equation because renal excretion measures the output



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*water soluble drugs= excreted easily
*Lipid soluble drugs= may need to be reabsorbed

Urinary pH trapping (Ion trapping)

Changing the pH of urine by chemicals can inhibit or enhance renal excretion of drugs.

Ion trapping is used to enhance renal clearance of drugs during toxicity.

Urine is normally slightly acidic and favors excretion of basic drugs.

Acidification of urine using ammonium chloride **(NH4Cl)** increases excretion of basic drugs as amphetamine.

Alkalinization of urine using sodium bicarbonate **(NaHCO3)** increases excretion of acidic drugs as aspirin.

Lipid soluble drugs are reabsorbed back and excretion will be low

Medium must be acidic(1-2)
So more basic drug can excreted via urine

—drug ph doesn't change
-medium PH will change forcing drug to be execrated
-chemicals must have no side effect

Polar drugs are readily excreted and poorly reabsorbed

- Acidic drugs are best excreted in alkaline urine(sodium bicarbonate).
- Basic drugs are best excreted in acidic urine(ammonium chloride).

Main route of excretion

1.Renal excretion

Drugs excreted mainly by the kidney include:

1. **very important here
   Aminoglycosides antibiotics (as gentamycin)
2. B-lactam antibiotics as penicillin
3. Lithium

Drugs should be <u>prescribed carefully in:</u>

1. patients with <u>renal disease</u>
2. Elderly people

2. Biliary excretion

occurs to few drugs that are excreted into feces

Drugs are secreted from the liver into bile by active transporters into duodenum

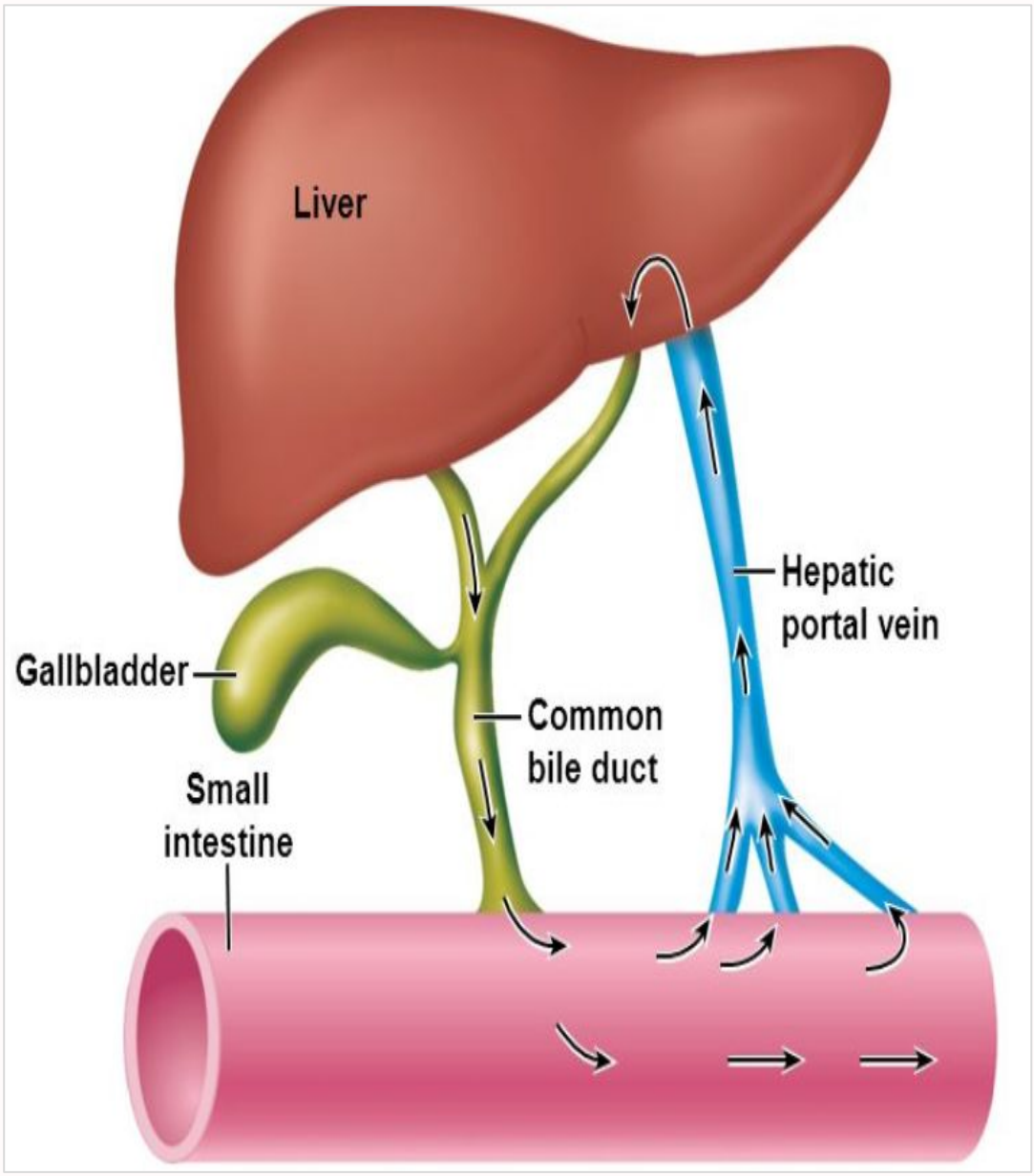
Enterohepatic
Entero=intestate
Hepatic=liver

-Some drugs undergo Enterohepatic circulation from intestine back into systemic blood circulation (where if moves back through the hepatic portal vein towards the liver then back to the systemic circulation again)

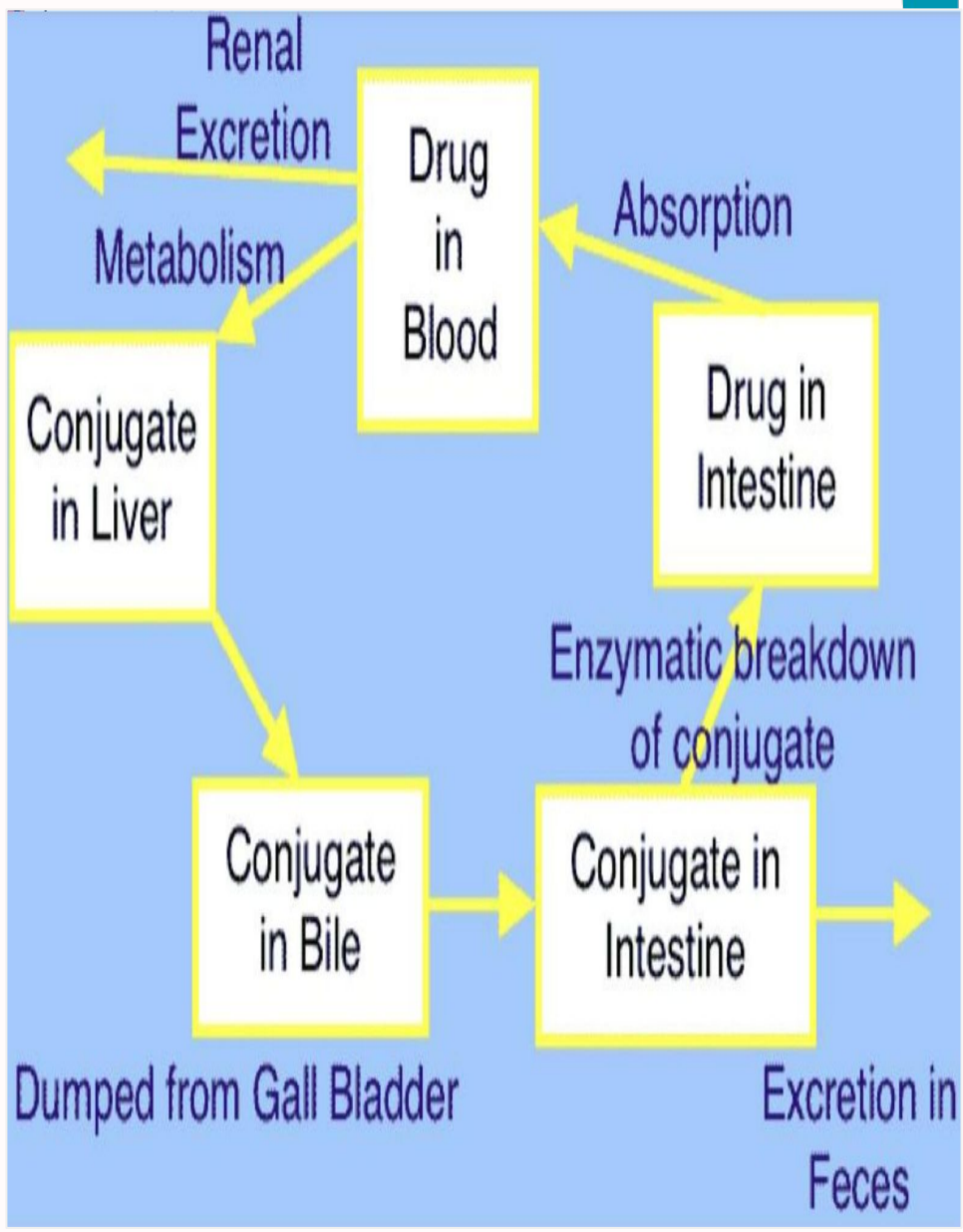
-Drugs excreted in the bile in the form of **glucuronides** will be hydrolyze in intestine by **bacterial flora** liberating free drugs which can be reabsorbed back into blood if the drugs are lipid soluble

-**this prolongs the duration of action of drugs**
e.g.
digoxin, morphine, thyroxine

Enterohepatic circulation



Excretion



In male slide only

plasma half-life (t ½)

Definition

it is the time required for the plasma concentration of a drug to fall to half of its initial concentration

- measures duration of action
- determine the dosing interval

factors that may increase half-life (t ½)

1-decreased metabolism	2-decreased clearance	3-High binding of drugs	4-Enterohepatic recycling
-Liver disease -Microsomal inhibitors	-Renal disease -Congestive heart failure	-Plasma proteins -Tissue binding	

Drugs of short plasma half life

❖ E.g Penicillin G, tubocurarine.

Drugs of long plasma half life

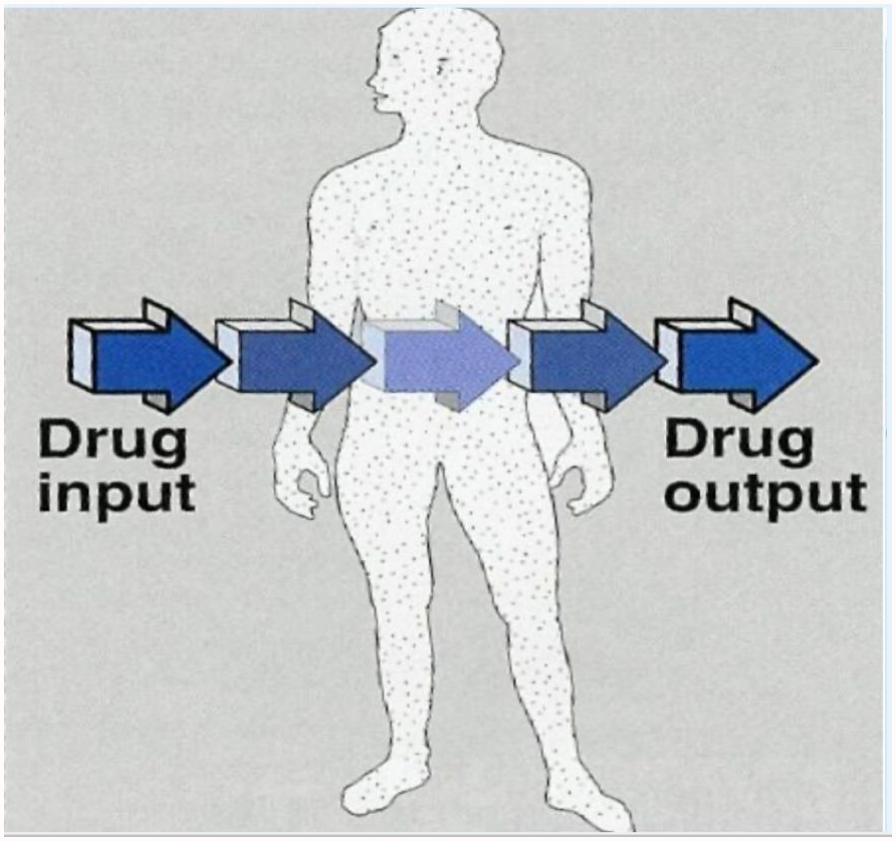
❖ E.g Digoxin, thyroxine.

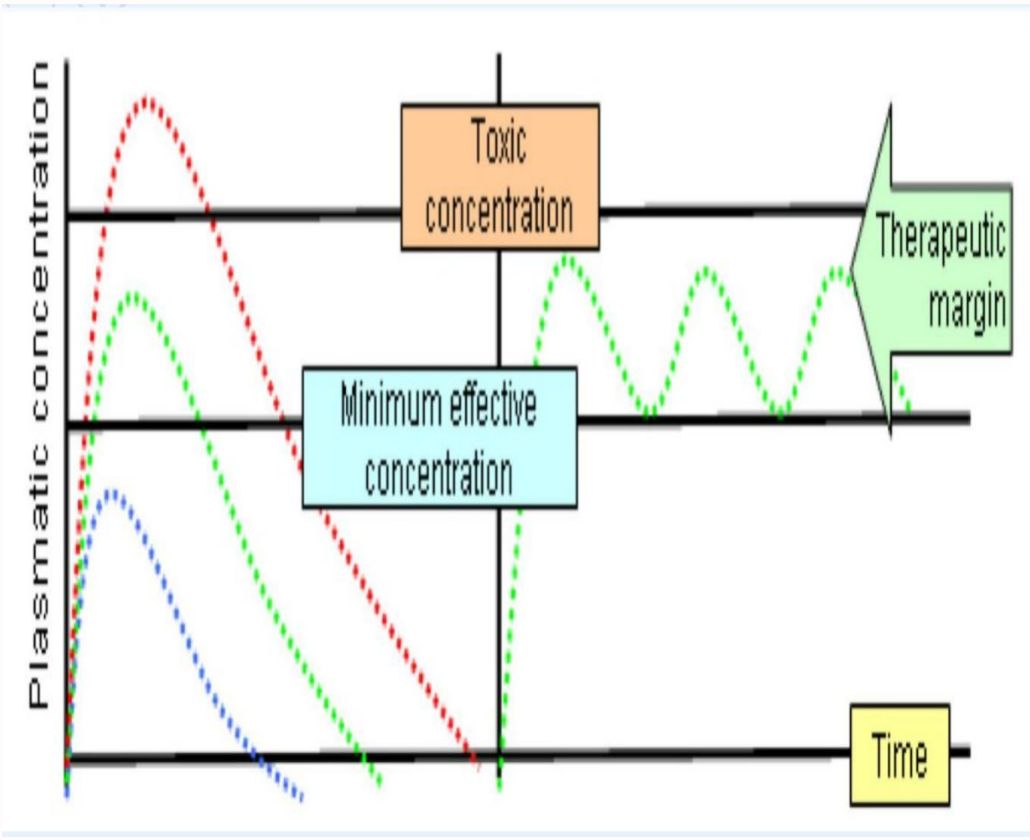
Click here for a useful video!

Steady state level

- Steady state level: A state at which the therapeutic plasma concentration of the drug (mg/ml) **remains constant within the therapeutic window.**
- Another definition: the amount of drug eliminated **equals** the amount of drug administered.
- Therapeutic window: the range between the effective and the toxic level of the drug

Rate of drug administration = Rate of drug elimination





Steady state level

How many half-lives would be necessary to reach steady state?

-Steady state concentration is attained after 3-5 half lives. E.g. Morphine

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

t ½=0 concentration of drug=100%

t ½=1
Concentration=50%

t ½=3
Concentration=87.5%
(37.5+50)

t ½=5
Concentration=97%
(47+50)

Dose 2

Dose 4

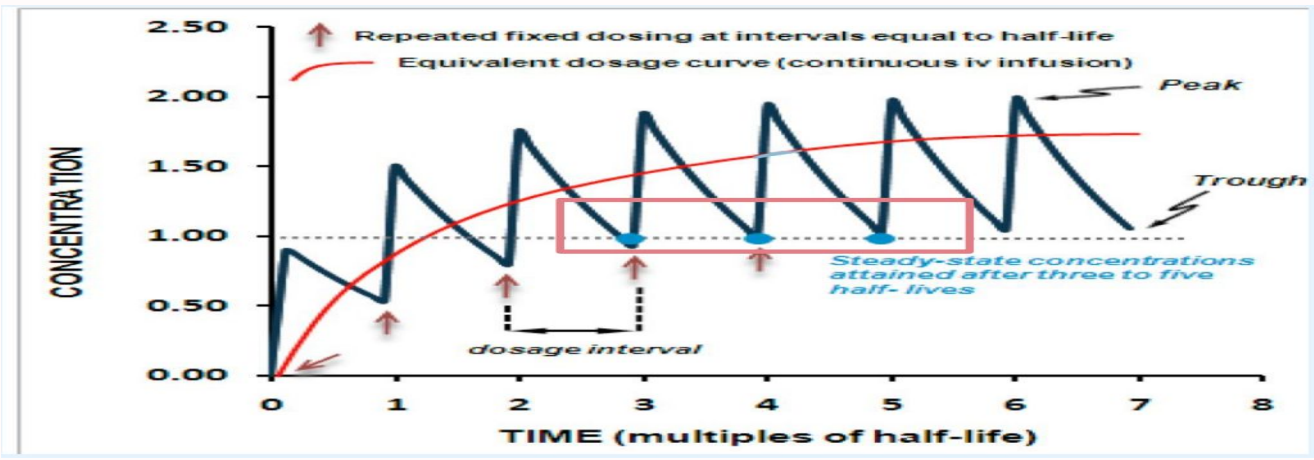
Dose 3

Dose 5

Dose 1

t ½=2
Concentration=75%
(25+50)

t ½=4
Concentration=94%
(43.8+50)



Loading dose	Maintenance dose
is the large initial dose that is given to achieve rapid therapeutic plasma level .	Are the doses required to maintain the therapeutic level of the drug constant or the steady state of the drug .
After administration of the drug, the plasma concentration decreases due to distribution of drug to other tissues .	These doses balance the amount of drug lost during metabolism and clearance
These doses balances the drug distribution .	The patient needs to take regular doses of drug such as amoxicillin (500 mg)/8 hours to maintain the therapeutic level .
This is important for drugs with long half lives and emergencies Loading dose = Vd x required plasma drug concentration	Maintenance dose = Clearance x required plasma 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 required in the condition being treated.
- e.g. lidocaine is antiarrhythmic drug with t ½ of around 1-2 hours .
- Arrhythmias after myocardial infarction are life threatening , and one cannot wait more several hours to achieve a therapeutic concentration .
- Use of loading dose of lidocaine in coronary care unit is standard

Steady state = 3-5 x 2 hours = 6-10 hours

MCQs

Q1. You administer to a patient an oral maintenance dose of drug calculated to achieve a steady-state plasma concentration of 5 mcg/L. After dosing the patient for a time sufficient to reach steady state, the average plasma concentration of drug is 10 mcg/L. A decrease in which of the following parameters explains this higher than anticipated متوقع plasma drug concentration?			
a) Bioavailability	b) Volume of distribution	c) Clearance	d) half life

Q2. One of the MAIN routes of excretion			
a) Tears	b)Skin	c)Pulmonary	d)Renal

Q3. We use ..... for Acidification			
a)NH4CL	b)NaHCO3	c)H2o	d)Penicillin

Q4. If a drug has a half life of 2 hours, how long will it take to reach the steady state?			
a)2 hours	b)8 hours	c)16 hours	d)32 hours

Q5.is the large initial dose that is given to achieve rapid therapeutic plasma level?			
a)loading dose	b)Maintenance dose	c)Overdose	d)dose

Answers:

1)C
2)D
3)A
4)B
5)A

SAQs

Q1.How many half-lives would be necessary to reach steady state?

?

3-5 half lives

Q2. Mention the types of active tubular secretion? And give
one example of each type?

?

Slide 5

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