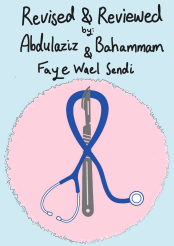


MED441
KING SAUD UNIVERSITY

Drug Excretion

Important
Main Text
Male slides
female slides
Extra information
Doctors notes

For any future corrections Editing file

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

Objectives

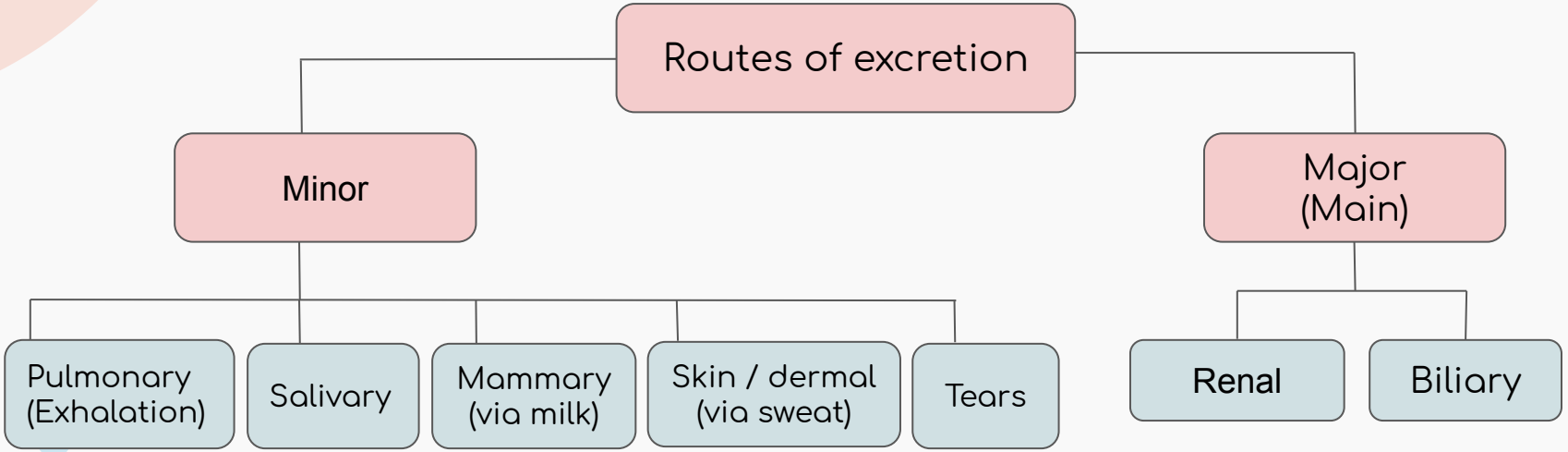
By the end of this lecture , students should be able to :

- 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 ½) , multiple dosing ,steady state levels , maintenance dose and loading dose.

Excretion of drugs



Structure of kidney (Renal excretion)

- The structure unit of kidney is **nephron** that consist of :
  - Glomerulus
  - Proximal convoluted tubules
  - Loop of Henle
  - Distal convoluted tubules
  - Collecting ducts

Renal excretion includes

Renal Excretion = filtration - Reabsorption + secretion

The principle process that determine the urinary excretion of drugs :

Glomerular Filtration Rate (GFR)

-Depends upon renal blood flow (600 ml/min).
-GFR 20% of renal blood = 125 ml/min.(the rest gets reabsorbed).
-Glomerular filtration occurs to :
-low molecular weight drugs
-only free drugs (unbound to Plasma protein) are filtered.

Passive tubular reabsorption

-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.

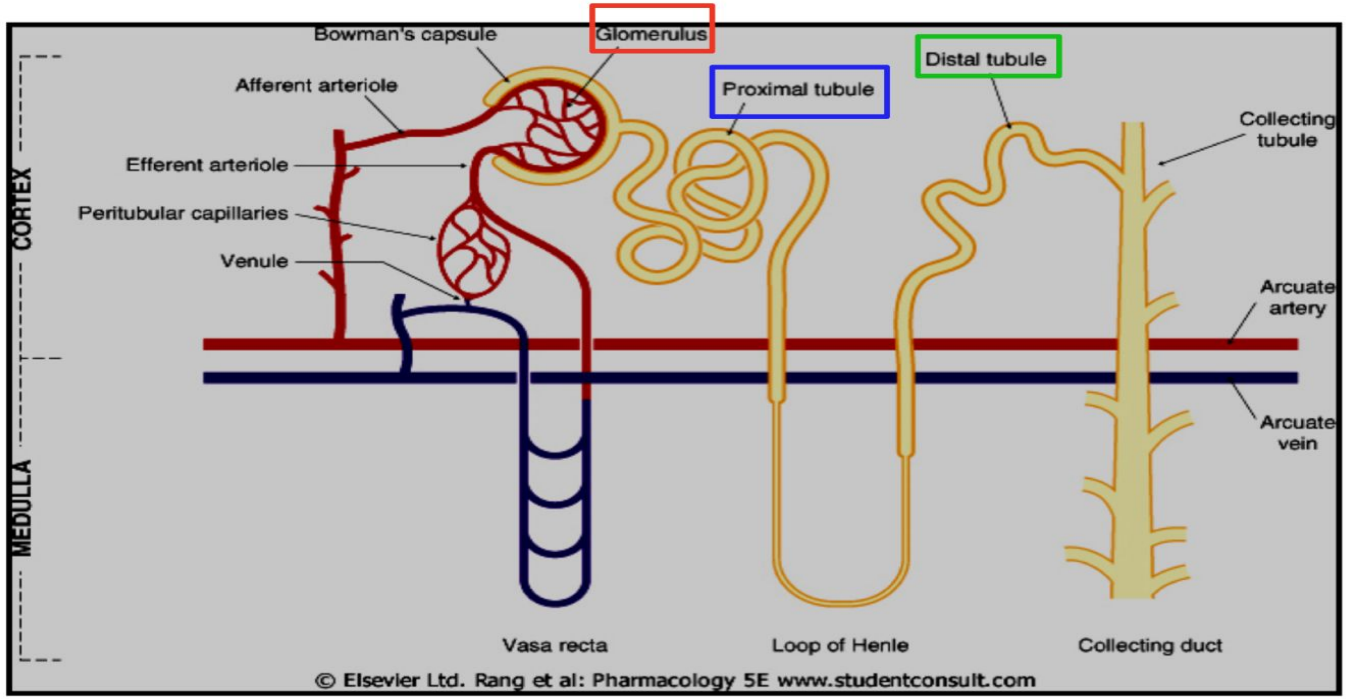
Active tubular secretion

-Occurs mainly in proximal tubules ; increases drug concentration in tubular lumen.
-Organic anionic and cationic transporters mediate active secretion of anionic and cationic drugs.
-Can transport drugs against conc. gradients.
-Example of actively secreted drug is penicillin

System for acidic drugs.
-salicylates e.g aspirin
-sulphonamides
-penicillin
-Transport of acidic drugs is blocked by probenecid

System for basic drugs.
-Morphine
-Atropine
-Quinine
-Neostigmine

Suffix **ine** = the drug is **basic**, and **has N atoms** , can cross **BBB** and produce **CNS** action, can reach fetus

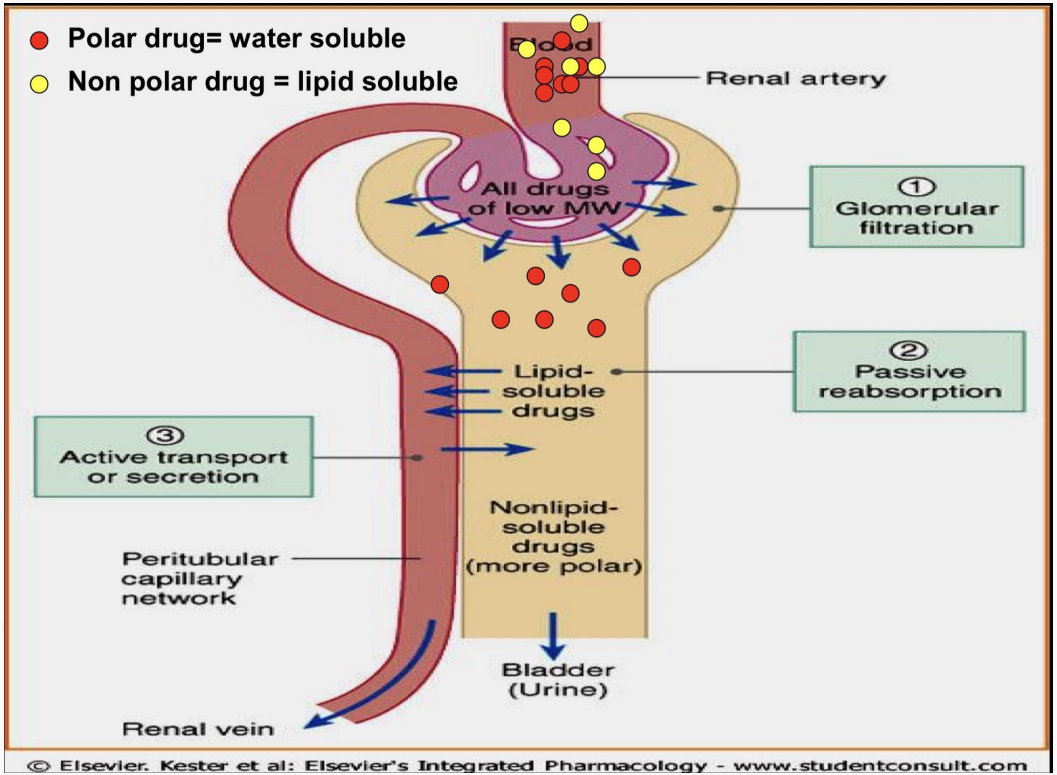


- Glomerular Filtration Rate (GFR): 1-low weight 2-Free drugs
- Proximal tubule: anionic and cationic transporters
- Distal tubules: ionized molecules

ال unionized molecules رجعت لل blood circulation عشان يصير
لها metabolism phase II وتصير بال ionized form

Renal Excretion

Renal Excretion (Total out) = Filtration(Out) **-** Reaabsorption(In) **+** Secretion(Out)



Note : the reabsorption is a negative value in the equation because renal excretion measures the OUTput

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

Changing the pH of urine by chemicals can: **inhibit or enhance** the renal excretion of drugs. or **inhibit or enhance** the drug reabsorption from renal tubules back into blood circulation.

Urine is **normally** slightly **acidic** and favor excretion of basic drugs

Urinary pH trapping (Ion trapping)

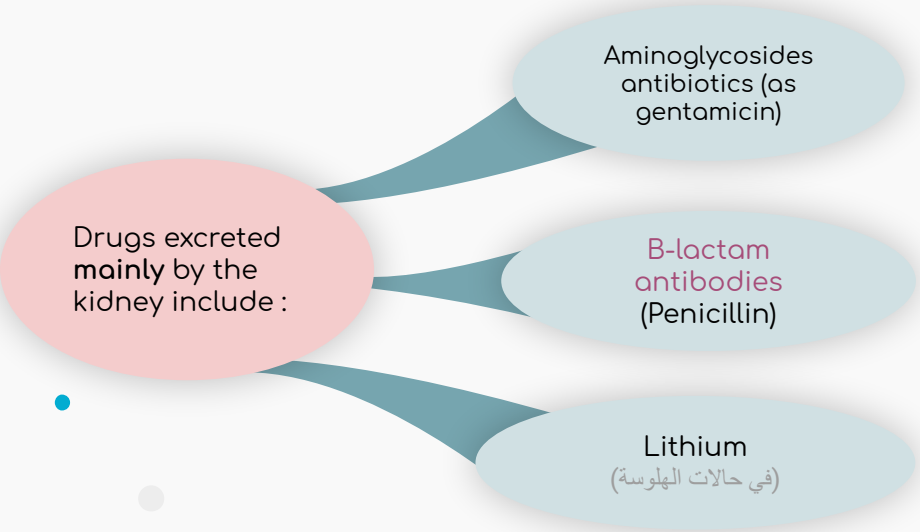
Acidification of urine using **ammonium chloride (NH4CL)** increases excretion of basic drugs .
Ex: amphetamine

Alkalinization of urine using **sodium bicarbonate (NaHCO3)** increases excretion of acidic drugs .
Ex: Aspirin

Note :
-Acidic drugs : best absorbed in acidic medium , best excreted in basic medium.
-Basic drugs : best absorbed in basic medium , best excreted in acidic medium.

Main routes of excretion

1-Renal Excretion



These drugs should be prescribed carefully for:

-Patient with renal disease.

-Elderly people.

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

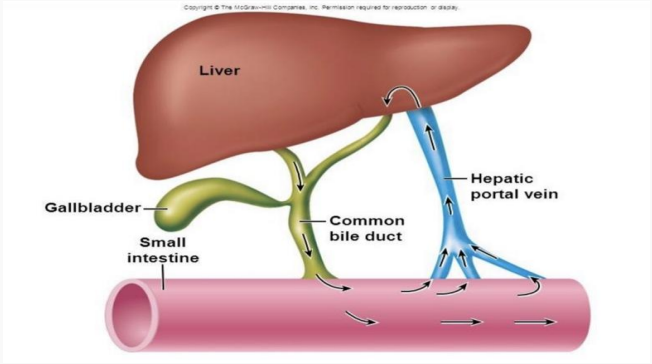
Main routes of excretion

2-Biliary Excretion

Occurs to few drugs that are **excreted into feces.**

It has **two** types

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



Drugs undergo enterohepatic circulation (Where they move back through the hepatic portal vein towards then **back to the systemic circulation**)

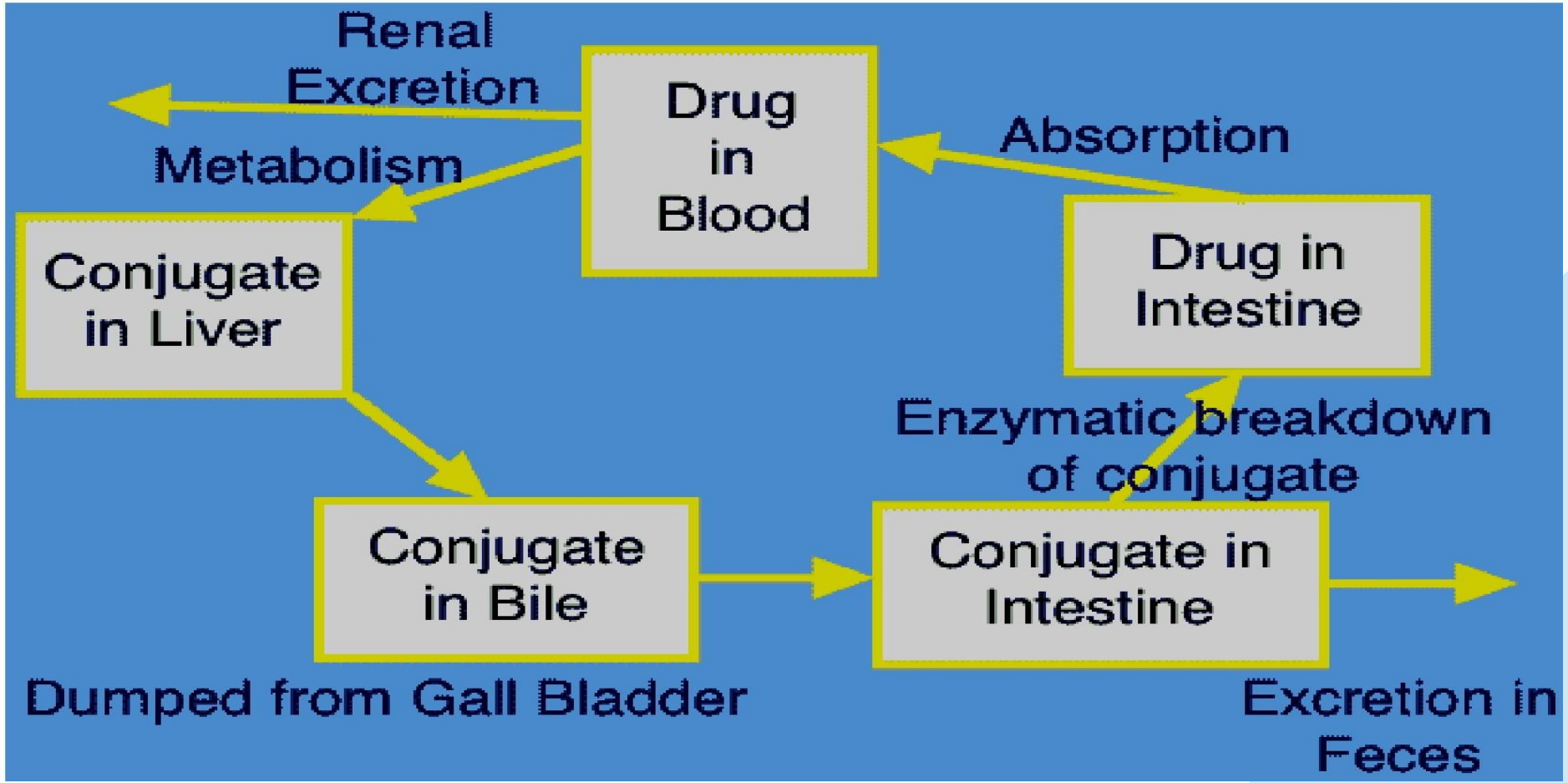
-Drugs excreted in the bile in the form of glucouronides will hydrolyzed in intestine by bacterial flora liberating free drugs that can be reabsorbed back into blood if the drugs are lipid soluble

-This prolongs the duration of action of drugs

. Ex : digoxin, morphine and thyroxine.

Enterohepatic
Entero = intestate
Hepatic = liver

Excretion


Renal Excretion
Drug in Blood
Absorption
Metabolism
Conjugate in Liver
Drug in Intestine
Enzymatic breakdown of conjugate
Conjugate in Bile
Conjugate in Intestine
Dumped from Gall Bladder
Excretion in Feces

Plasma half-life (t $\frac{1}{2}$)

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

Is a measure of duration of action.

Determine the dosing interval

Drugs of short plasma half life.

- Penicillin G, tubocurarine.

Drugs of long plasma half life.

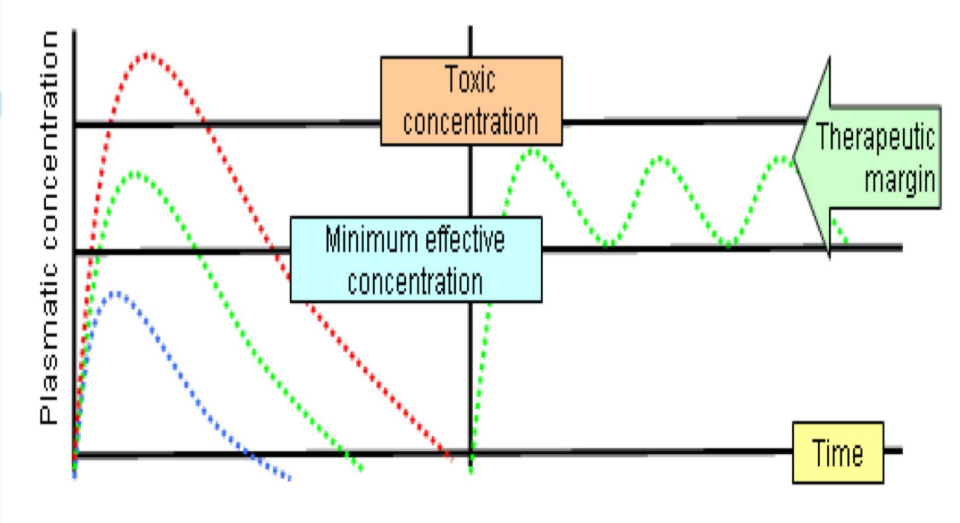
- Digoxin, thyroxine.

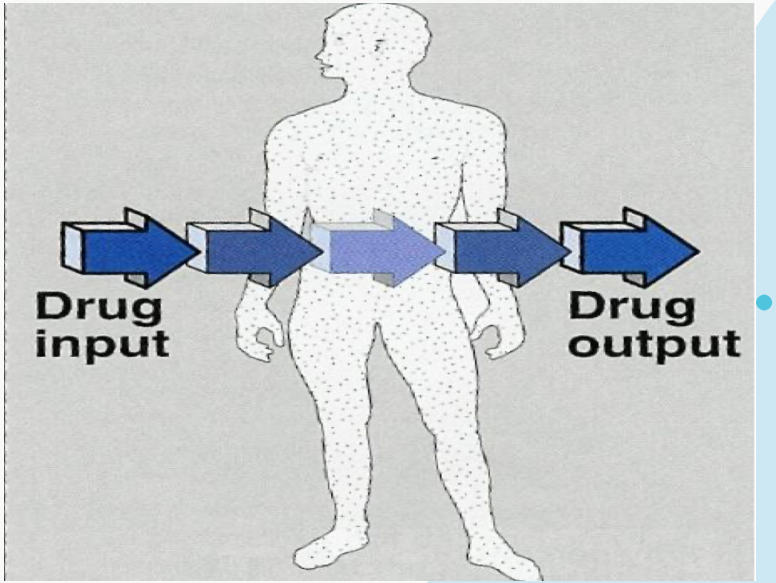
➢ Factors that may increase half-life (t $\frac{1}{2}$)

01	Decreased metabolism	• Liver disease. • Microsomal inhibitors.
02	Decreased clearance	• Renal disease. • Congestive heart failure.
03	High binding of drugs	• Plasma proteins. • Tissue binding.
04	Enterohepatic recycling	

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.
- **At steady state:** Rate of drug administration = Elimination rate
- **Therapeutic window:** the range between the effective and the toxic level of the drug.

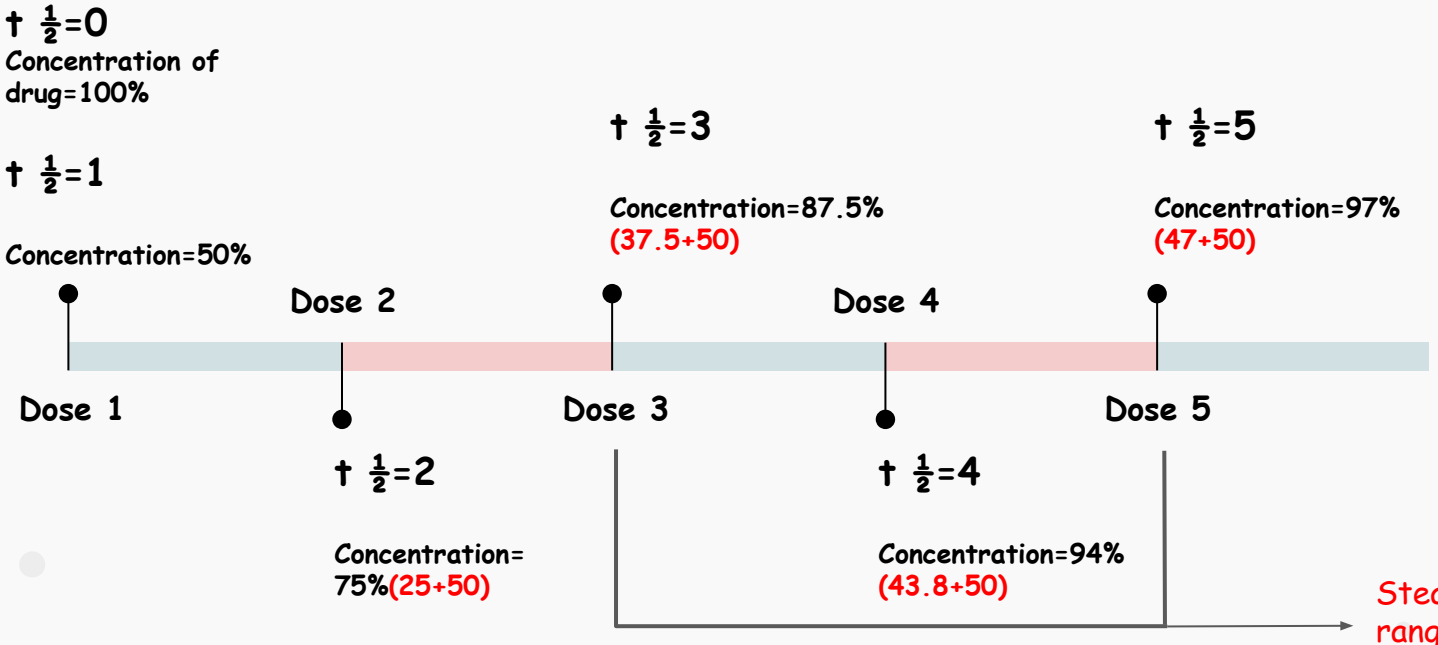




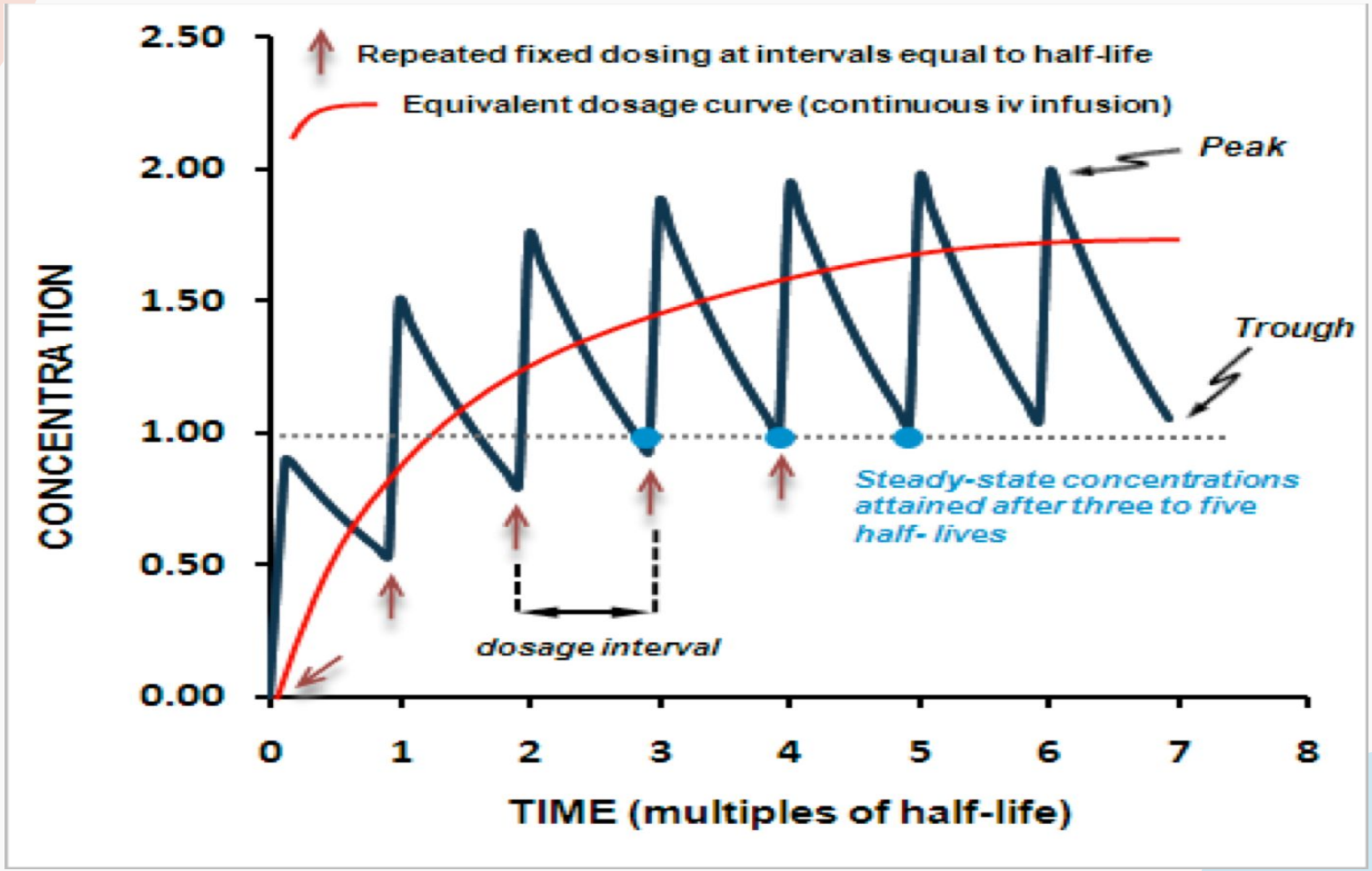
How many half-lives would be necessary to reach steady state?

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

t ½ 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 diagram is only in female slides


Repeated fixed dosing at intervals equal to half-life
Equivalent dosage curve (continuous iv infusion)
Peak
Trough
Steady-state concentrations attained after three to five half- lives
dosage interval
CONCENTRATION
2.50
2.00
1.50
1.00
0.50
0.00
0
1
2
3
4
5
6
7
8
TIME (multiples of half-life)

helpful video

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 a 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

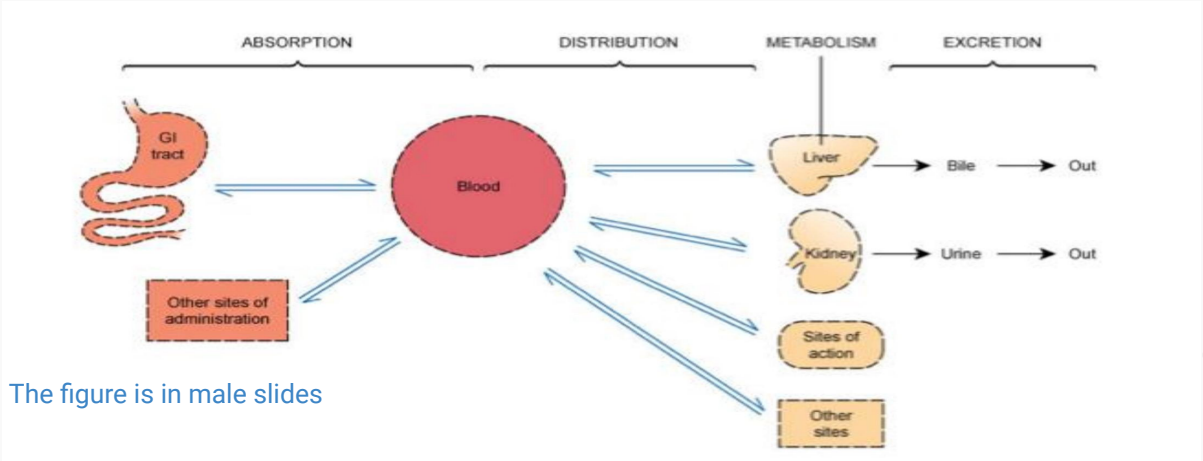
Clinical applications of loading dose

- A loading dose may be desirable if the time required to attain steady state of drug (4 elimination t $\frac{1}{2}$ values) is long and rapid relief is required in the condition being treated.
- e.g. lidocaine is antiarrhythmic drug with t1/2 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 a loading dose of lidocaine in the coronary care unit is standard.

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

Summary

- Polar drugs are readily excreted and poorly reabsorbed.
- Lipid soluble drugs are reabsorbed back and excretion will be low.
- Acidic drugs are best excreted in alkaline urine (sodium bicarbonate).
- Basic drugs are best excreted in acidic urine (ammonium chloride).
- Enterohepatic circulation prolongs half life of the drug.



The figure is in male slides

Quiz

1. Passive tubular reabsorption happens in :

A)Proximal convoluted tubules

B)Distal convoluted tubules

C)Collecting ducts

D)Both B+C

2. Basic drug best absorbed in(.....)medium , best excreted in(.....)medium.

A)Acidic / Basic

B)Basic / Acidic

C)Acidic / Acidic

D)Basic / Basic

3.All of the following drugs are basic drugs except :

A)Morphine

B)Quinine

C)penicillin

D)Atropine

4.Which factor may decrease half life (t1/2)

A)decreased metabolism

B)high binding of drug

C)Low binding if drug

D)Enterohepatic circulation

1.D 2.B 3.C 4.C

Quiz

5.Drug with a short half life :

A)thyroxine.

B)lidocaine .

C)Digoxin.

D)amiodarone

6. the range between the effective and the toxic level of the drug:

A)Maintenance dose

B)steady state

C)Therapeutic window

D)Both B+C

7.Concentration of the drug after the third dose :

A)87.5%

B)94%

C)75%

D)97%

8.Drugs are secreted from the liver into bile into :

A) ileum

B)urinary bladder

C)jejunum

D)duodenum

5.B 6.C 7.A 8.D

Thank you

Team leaders

Lujain Alkhalaf - Salman Alotaibi

Female team members:

- Alanoud Albawardi
- Shaimaa Alqaoud
- Nada Alsaif
- Raneem Alanazi
- Ftoon Alenazi
- Areej Altamimi
- Sarah Alotaibi
- Rand Alshaya
- Rand Aldajani

Male team members:

- Anas Alharbi
- Abdulrahman Alghamdi
- Abdullah Alotaibi
- Abdulaziz Aqusaiyer
- Bader Alshahrani
- Saad Alghadir
- Abdullah Alghamdi
- Mohammed Alsaqabi
- Abdulrahman Badghaish

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