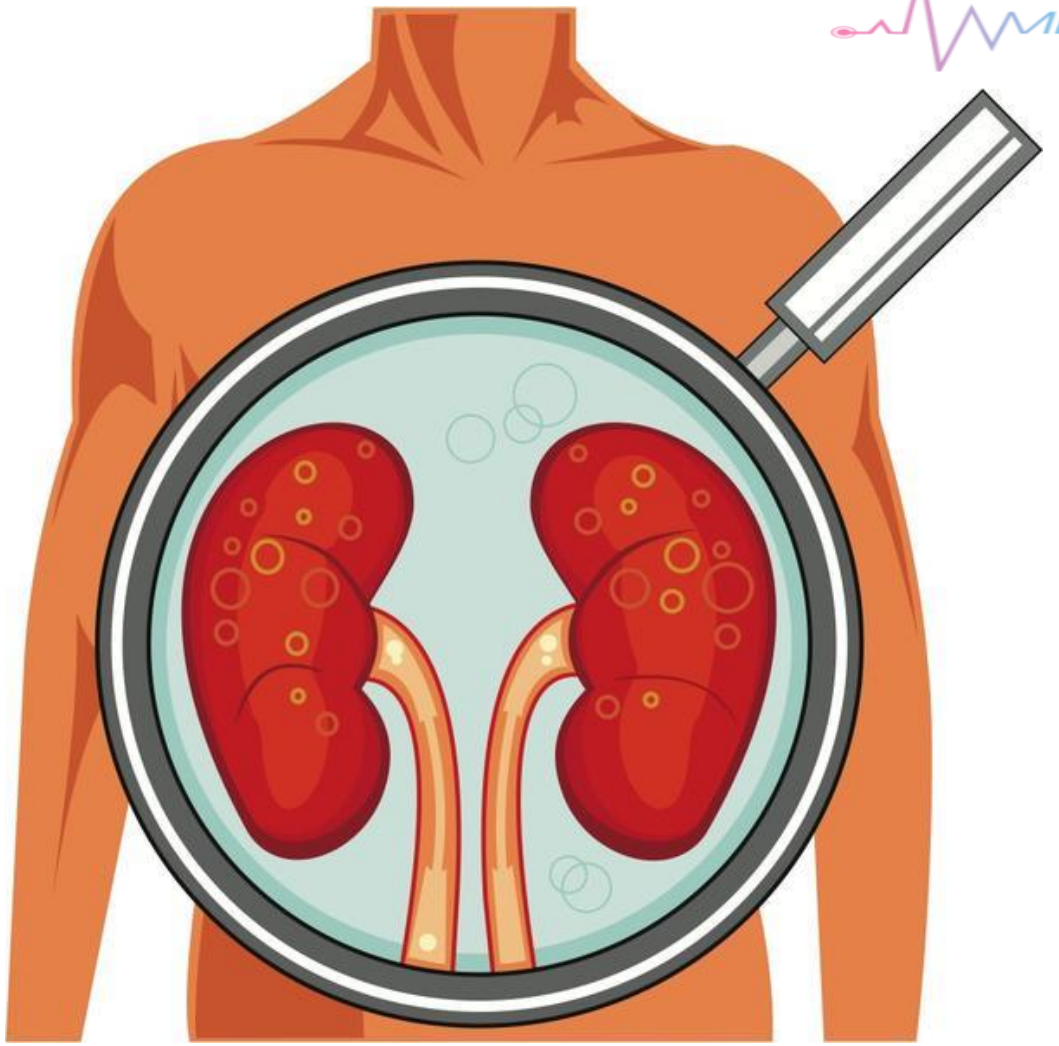
1

Renal Excretion of Drugs.

Renal block.

Additional note : Grey color.



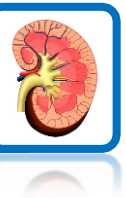
For any correction, suggestions or any useful information do not hesitate to contact as: Pharmacology434@gmail.com

If you want to understanding better , You can Review the excretion lecture of the Pharmacokinetics from the Foundation Block

Routes of Excretion:

- Major:
  - 1- Renal
  - 2- Biliary
- Minor:
  - 1- Pulmonary.
  - 2- Salivary.
  - 3- Mammary " via milk".
  - 4- Skin / Dermal " via sweat".

- The most important organ for drug excretion is the kidney.



Normal Kidney Functions:

Regulation:

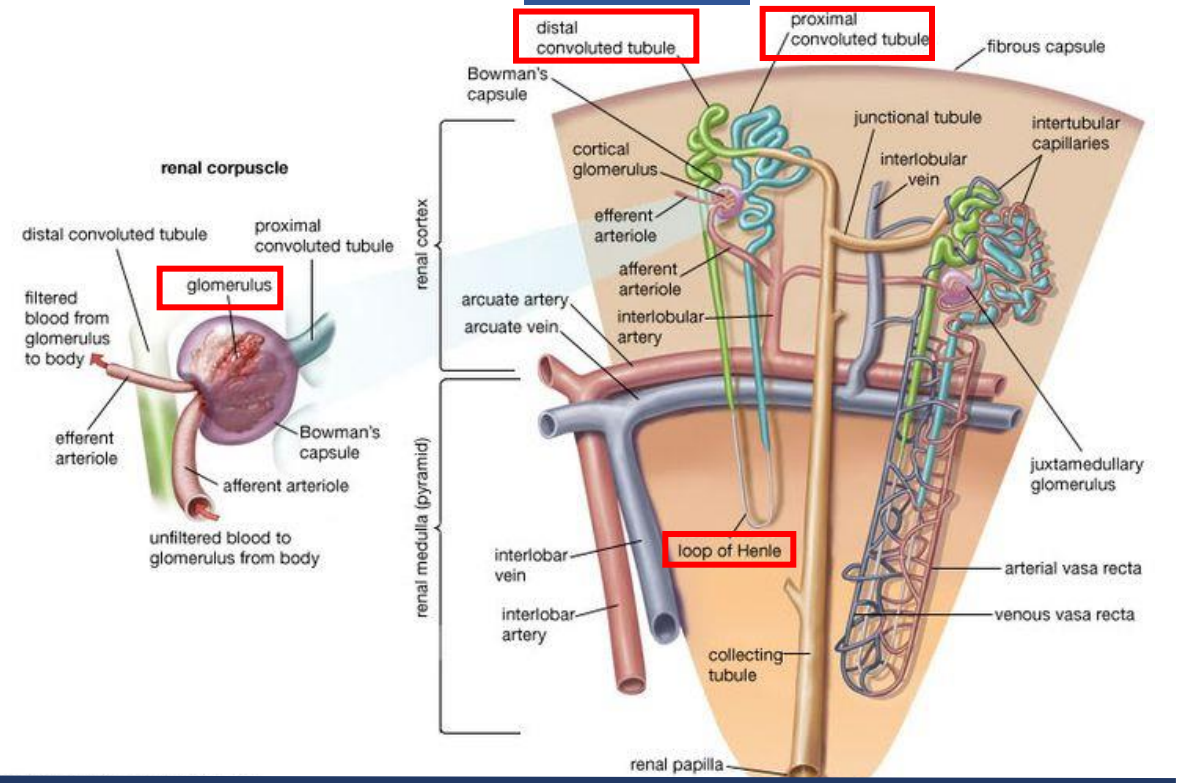
- electrolytes (aldosterone).
- water balance (anti-diuretic hormone).

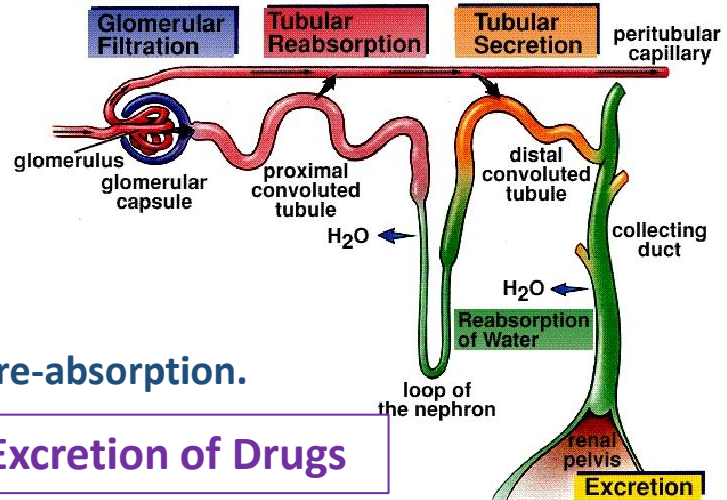
Excretion:

- wastes & drug metabolites such as :
  - Urea
  - Uric acid
  - Creatinine

Structure of Kidney:

The structural unit of kidney is **nephron**, That consists of:





Occurs Through 3 Processes:

1- Glomerular filtration.

2- Active tubular secretion.

3- Passive or active tubular re-absorption.

Urinary Excretion of Drugs

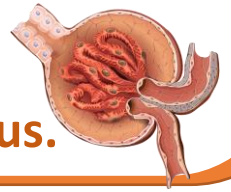
1- Glomerular Filtration (GF)

-**Where it occurs?** Blood is filtered across a semi-permeable membrane into the Bowman's Capsule.

- **Driving force** for GF is hydrostatic pressure of blood flowing in capillaries.

- **Filtrate contains** water, glucose, amino acids, sodium bicarbonates, organic solutes and electrolytes (sodium, potassium, chloride).

- **What does not get filtered?** Blood cells, platelets, and plasma proteins are retained in the blood and not filtered.



- Most drugs are filtered through **glomerulus.**

-Rate (GFR):

- **Definition:** The amount of blood filtered by the glomeruli in a given time.
- Normal GFR = 125 ml/min.
- **GFR is used as** a marker or indicator for kidney function.
- **GFR is determined by** Creatinine, Inulin (Inulin is easily filtered by kidney not reabsorbed).
- Creatinine clearance (CrCl) is used as a marker instead of GFR.

of Drugs Occurs to:

- **Low molecular weight drugs.**
- **Water soluble drugs** e.g. Aminoglycosides, Tubocurarine free form of the drugs (not bound to plasma proteins).
- **free form of the drugs (not bound to plasma proteins).**
- **Drugs with low Volume of distribution (Vd).**

(Glomerular filtration depends mainly on renal blood flow. So, if a patient has a disease that affects renal blood flow → Glomerular filtration will be affected, E.g. patient with CHF)

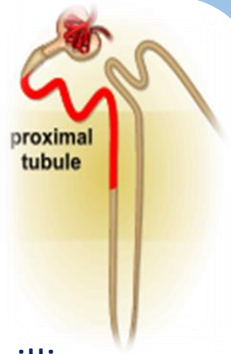
(Drugs with low volume of distribution (Vd): meaning that it is more concentrated in blood and less in tissues. This will increase the amount of drug delivered to the kidneys)

2- Active Tubular Secretion of Drugs:

-Occurs mainly in proximal tubules

-It increases drug concentration in the filtrate.

-Drugs undergo active secretion have excretion rate values greater than normal GFR.



-Secretion of ionized drugs into the lumen, e.g. penicillin.

(Active tubular secretion of drugs = From blood to filtrate)

Characters :

1- Needs energy.

2- Transports drugs against concentration gradients between blood and filtrate.

3- Requires carriers (transporters).

4- Saturable. **(We have a specific number of carriers and if they were occupied the process will stop)**

5- Not specific (competition may happens).

Types of Transporters:

- **Transporters for organic acids :**
  e.g. Penicillin, aspirin, sulfonamides, Probenecid.

- **Transporters for organic bases:**
  e.g. morphine, catecholamines, atropine, quinine.

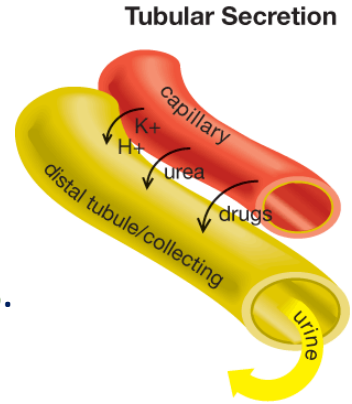
(Transporters for organic acids or transporters for organic bases: remember that acids will have the same transporter and bases will have the same transporter → competition on that transporter (acid transporter or base transporter) will occur and this can beneficial or harmful to the patient)

-Two drugs can compete for the same carrier e.g. Probenecid & penicillin, Probenecid & Nitrofurantoin.

Competitive Active Tubular Secretion of Drugs:

- 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 excretion will retard the excretion of other drug with which it **competes**.
- The half life of both drugs is **increased** since the total sites for active secretion are **limited**.



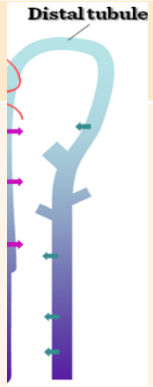
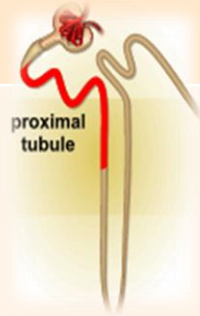
Beneficial Competition:	Harmful Competition:
- Probenecid & penicillin, both require the same carrier for renal excretion, - **Probenecid** competes with or retards renal tubular secretion of **penicillin.** - and thus less amount of **penicillin** will be excreted → **prolonged duration** of action of penicillin & increase in its antibacterial action.	- Probenecid & Nitrofurantoin. - Probenecid inhibits renal tubular secretion of Nitrofurantoin. - thus **decreases** its efficacy in urinary tract infections (UTIs). (Probenecid: is a drug used in UTIs. To be affective it has to be excreted (renal excretion). Probenecid and Nitrofurantoin: this combination should not be used)

3- Tubular Re-absorption of Drugs

- After glomerular filtration, drugs may be reabsorbed from tubular lumen back into systemic blood circulation.

- It takes place along all the renal tubules.

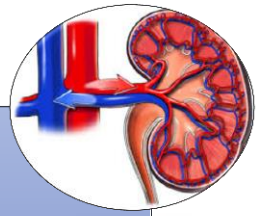
- Re-absorption
  - increases half life of a drug.
  - may be passive or active. (Re-absorption: depends on wither the drug is water or lipid soluble)

	Passive Tubular Re-absorption of Drugs:	Active Tubular Re-absorption of Drugs:
Location:	- In distal convoluted tubules & collecting ducts. 	Mainly in proximal tubules. 
Function:	**Non-ionized drugs: (Only lipid soluble drugs)** - undergo passive tubular re-absorption from tubular lumen back into blood (not excreted in the urine, urinary excretion will be low). **Ionized drugs (water soluble) :** are poorly reabsorbed, excreted easily in the urine, and urinary excretion will be high.	- It occurs with endogenous substances or nutrients that the body needs to conserve. e.g. glucose, electrolytes, amino acids, uric acid, vitamins.
Example:		**- Probenecid** acts as a uricosuric agent in the treatment of gout. - It increases excretion of uric acid in urine by inhibiting active tubular re-absorption of the endogenous metabolite uric acid.

Factors affecting renal excretion of drugs

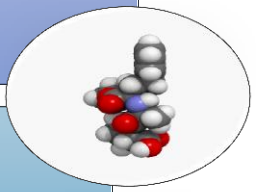
Renal blood flow

*Adequate renal function depends upon renal blood flow.
*Decline in renal blood flow can decrease excretion of drugs.
*NSAIDS e.g. aspirin and ibuprofen inhibit the production of prostaglandins and therefore reduces renal perfusion and GFR.
Prostaglandins: in the kidney they increase renal blood flow.



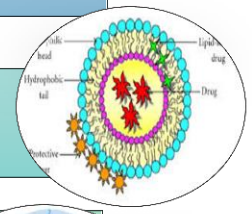
Molecular weight of the drug

Larger MW drugs are difficult to be excreted than smaller MW especially by glomerular filtration .



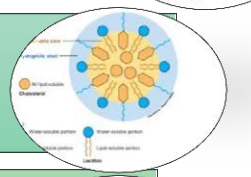
Lipid solubility of drugs

*Urinary excretion is inversely related to lipophilicity.
*Increased lipid solubility increases volume of distribution of drug and decreases renal excretion.



Degree of ionization of drugs

*Increased ionization of drug increases its water solubility and thus enhances its renal excretion.
*Polar or water soluble drugs are easily filtered e.g aminoglycosides, tubocurarine

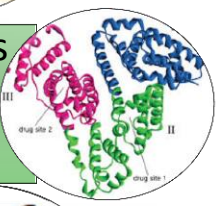


Volume of distribution

*Renal clearance is inversely related to volume of distribution of drugs (Vd).
*Drugs with large Vd are poorly excreted in urine.
*Drugs restricted to blood (low vd) have higher renal excretion rates.

Binding characteristics of drugs

*Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus.
*Only unbound form of drug (free form) appears in glomerular filtrate.
*Protein bound drugs have long half lives.



Biological factor

*Age can affect renal clearance.
*Renal clearance is reduced in neonates and elderly due to pharmacokinetic changes.
*Dose reduction is advisable otherwise toxicity may occur.

Renal Excretion of drugs in neonates

*More total body water than adults.
*Greater volume of distribution of water-soluble drugs.
*Lower concentration of drug in the blood coming to the kidneys and decreased rate of drug clearance.
↓renal blood flow in newborn
↓ glomerular filtration of drugs.

Effects of Aging on the Kidney (in Elderly)

* ⇓ kidney size
* ⇓ renal blood flow
* ⇓ number of functional nephrons.
* ⇓ tubular secretion
* Result: ⇓ glomerular filtration rate (GFR)
* Decreased drug clearance

Diseases states

Impairs the elimination of drugs thus may increase half-life (t ½) of drugs. This may occur due to

Reduced renal blood flow

*Congestive heart failure.
*Hemorrhage
* Cardiogenic shock

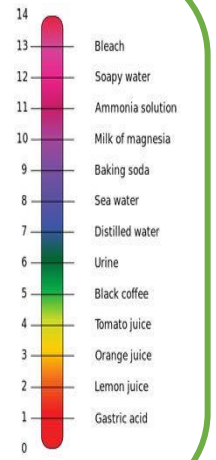
Decreased renal excretion :

Renal disease (e.g. glomerulonephritis).

Renal excretion of drugs and pH of urine

*Most drugs are weak acids or weak bases
*Normal urine (pH 5.3) slightly acidic and favors excretion of basic drugs.
*Most of acidic drugs will be reabsorbed back into body.
*Change pH of urine can inhibit or enhance the passive tubular re-absorption of drugs.

Note : Basic drugs in acidic environment (urine) will be in the ionized form (water soluble) –> will be excreted.
While acidic drugs in acidic environment (urine) will be in the non-ionized form (lipid soluble) -> re-absorption.

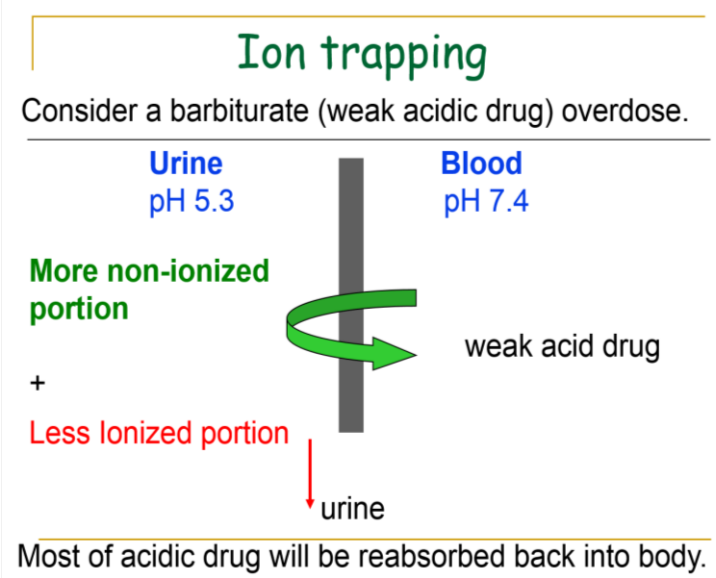


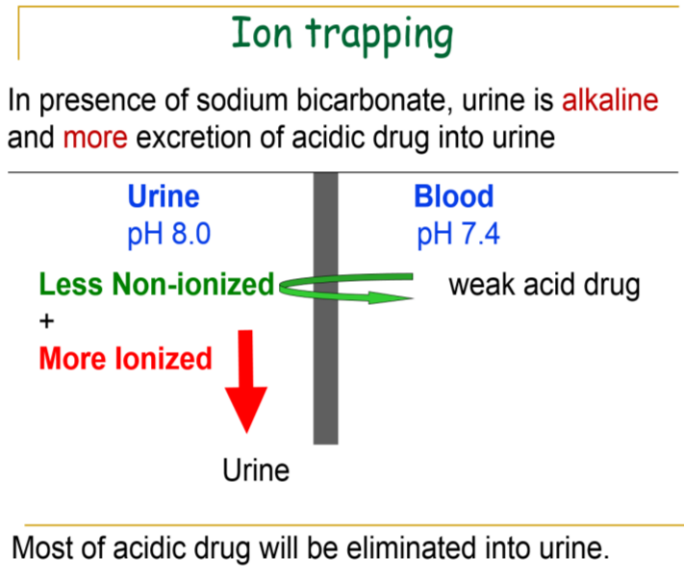
Urinary pH trapping (Ion trapping)
It is used to enhance renal clearance of drugs during toxicity.

Urine acidification: by ammonium chloride (NH4Cl) increases excretion of basic drugs (amphetamine).

Urine alkalization: by sodium bicarbonate NaHCO3 increases excretion of acidic drugs (aspirin).

Note :If toxicity occurs from drug taken orally we can do gastric lavage. But if it was from drug taken by IV injection we can choose between: hemodialysis or ion trapping (forced diuresis) to promote renal clearance of the drug.





Creatinine clearance and drugs excretion

* Creatinine clearance rate (CrCl) is the volume of blood that is cleared of creatinine per unit time.
* Creatinine clearance (CrCl) is used to estimate glomerular filtration rate (GFR) because creatinine is produced from muscle and freely filtered (low MW, water soluble, and is not protein bound).

Renal clearance

$$CLr\ (ml/min) = \frac{\text{Excretion rate } [CuVu]}{\text{Plasma concentration } [Cp]}$$

CLr : renal clearance
Cu : drug concentration in the urine
Vu : volume of urine in 24 hours
Cp: drug concentration in the blood

Estimation of Creatinine Clearance

The Cockcroft-Gault equation for estimation of creatinine clearance

$$\text{Female: } CrCl = \frac{0.85\ (140 - age) \times \text{body weight}}{\text{serum creatinine} \times 72}$$

$$\text{Male: } CrCl = \frac{(140 - age) \times \text{body weight}}{\text{serum creatinine} \times 72}$$

Renal clearance of drugs

*If renal clearance is impaired, this may increase t ½ of drugs and may result into drug toxicity.
*Renal clearance is especially important for some drugs which are:

*Mainly excreted by the kidney
*Have narrow therapeutic index (e.g. lithium, digoxin, warfarin).

Drugs excreted mainly by the kidney include:

Antibiotics:
Penicillins, cephalosporins
Aminoglycosides (gentamycin)
Sulfonamides

NSAIDs e.g. aspirin

Lithium

Digoxin

Immunosuppressants (cyclosporine)

Anticancer drugs (cisplatin)

Be careful upon prescribing those drugs in:
Renal failure patients –
Elderly patients

So what should we do in renal impairment?

* Dose reduction of drugs is required (when creatinine clearance is below 60 ml/min).
* keep the usual dose but prolong the dosing intervals (e.g. gentamicin).
* decrease the dose without changing dosing intervals in case of drugs with narrow therapeutic index (e.g. digoxin)
* Monitor blood levels of drugs (therapeutic drug monitoring).

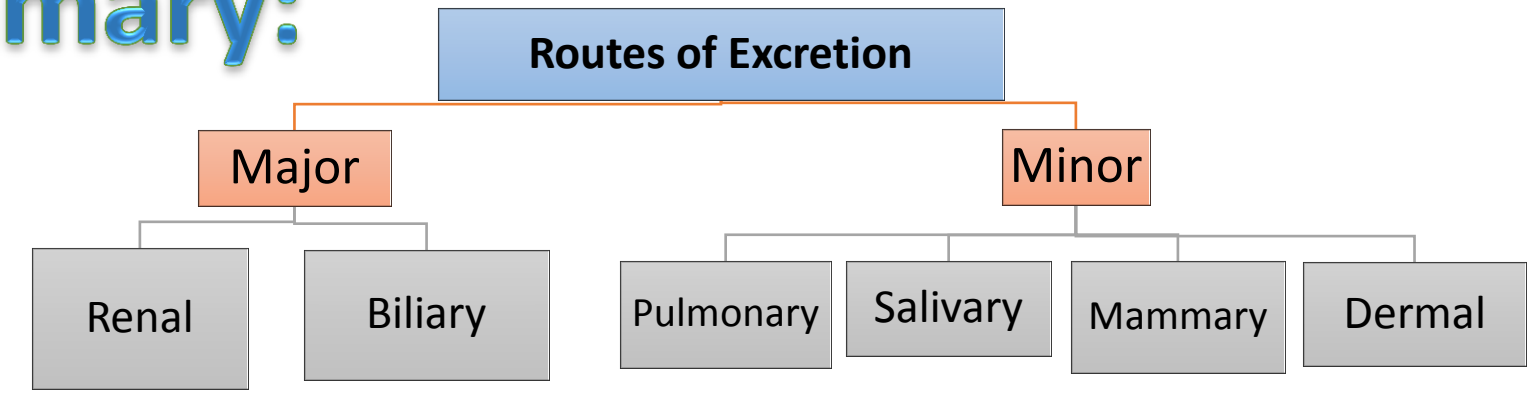
Creatinine clearance and drugs excretion

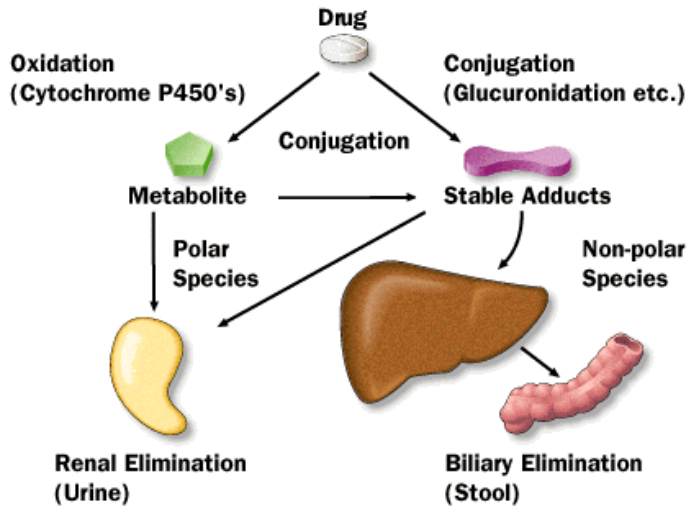
* Drugs that are primarily excreted by the kidney need dose adjustment.
* Minor dose adjustment if CrCl = 30-60 mL/min.
* Major dose adjustment if CrCl < 15mL/min

When dose reduction is not required in renal impairment ?

Few drugs e.g. ceftriaxone, minocycline that are excreted mainly into feces (biliary excretion) doesn't need dose adjustment in renal impairment.

Summary:





Principle processes of excretion

Glomerular filtration

- Blood is filtered across a semi-permeable membrane into the Bowman's Capsule
- Blood cells, platelets, and plasma proteins are retained in the blood and not filtered.
- Glomerular filtration of drugs occurs to: low MW of drugs, water soluble drugs, free from the drugs, drugs with low volume of distribution.

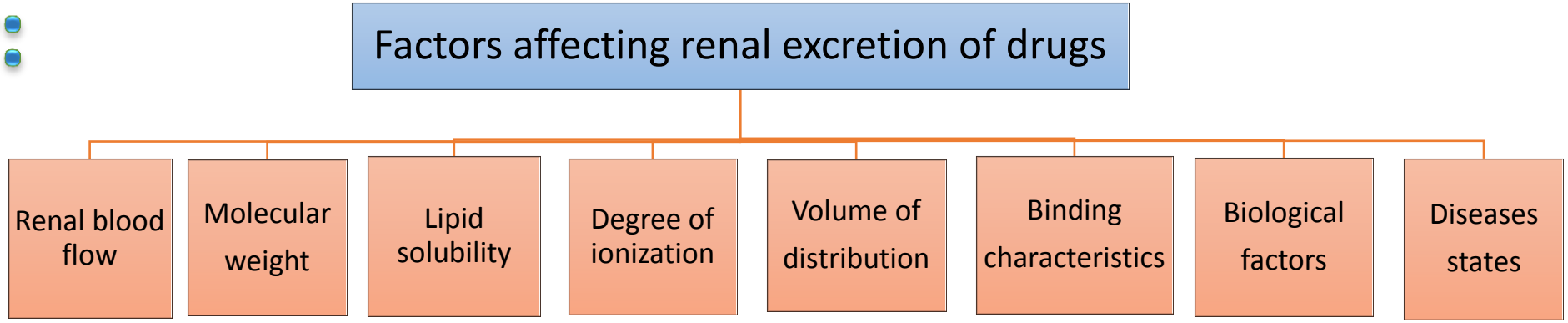
Active tubular secretion

-Occurs mainly in proximal tubules.
-Characteristics: needs energy, **against** concentration gradients, requires carrier (transporters), saturable, not specific (competition may happens).
-**e.g. Penicillin**

Passive or active tubular re-absorption

- It takes place all along the renal tubules.
- Re-absorption increases half-life of a drug.
- May be **passive** or **active.**

Summary:



Drugs and its characteristics

Probenecid	Act as uricosuric agent in the treatment of gout.
NSAIDS (Aspirin, Ibuprofen)	Inhibit the production of prostaglandins and therefore reduces renal perfusion and GFR.
Lithium, Digoxin, Warfarin	Have narrow therapeutic index.
Probenecid & Penicillin	Compete beneficial competition.
Probenecid & Nitrofurantoin	Compete harmful competition.
Aminoglycosides, Tubocurarine	Water soluble, polar, ionized drug.
Gentamicin	Keep the usual dose but prolong the dosing intervals.
Ceftriaxone, Doxycycline	Excreted mainly into feces (biliary excretion).
Penicillin, Aspirin, Sulfonamides, Probenecid	Acidic drugs.
Morphine, Catecholamines, Atropine, Quinine	Basic drugs.

MCQs

1-Which one of the following is never filtered ?

a) Glucose b) amino aids

c) Platelets d) all of above

2- to enhance the excretion of amphetamine we use :

a) NH4Cl to alkalize the urine

b) Sodium bicarbonate

c) Ammonium chloride to make the urine more acidic

3-When there is impairment we keep the usual dose but prolong the dosing intervals. With which drug we follow this method?

a) Gentamicin

b) Digoxin

c) Aspirin

4-Probenecide&nitrofurantion is an example of good competition:

a) True

b) False

5-Increased ionization of drug increases its renal excretion:

a) True

b) False

Answer: ***1-c 2-c 3-a 4-b 5-a***

SAQs:

1-What will happen when probencide competes with penicillin?

There will be longer half life of penicillin

2-the PH of urine is? *5.3*

3-Probencide is used in treatment of? *gout*

GOOD LUCK!

This Lecture was done by:

Lulu aldaej .
Malak alzhrani.
Elham algamdi.
Asma alrases.
Fetoon alnemari.
Ghada alouda.
Malak alkathlan.

For any correction, suggestions or any useful information do not hesitate to contact as: Pharmacology434@gmail.com