King Saud University
College of Medicine
1st Year, 5th Block

Renal Excretion of Drugs 3

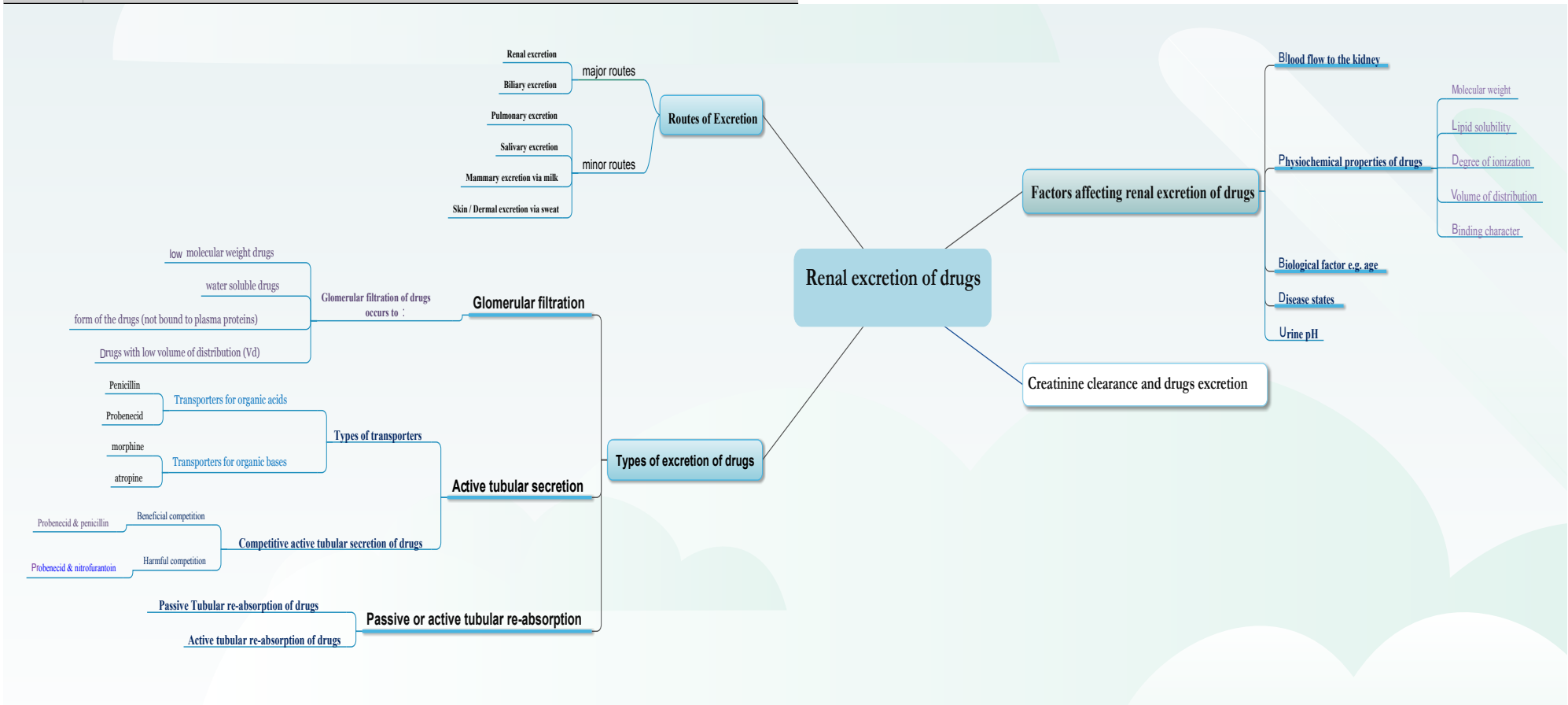
Renal Block

Objectives :

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

For better understanding:

Review the excretion lecture of the Pharmacokinetics from the Foundation Block :
[http://www.ksums.net/files/1st/01.Foundation%20Block/433%20Teams%20Work/Pharmacology/4-%20PharmacokineticsIV-Excretion.pdf]



Routes of excretion

Major :

A) Renal Excretion
By the Kidney

B) Biliary Excretion
By the liver

Minor :

*Pulmonary excretion (Exhalation)
*Salivary excretion
*Skin\Dermal excretion via sweat
*Mammary excretion via milk
*Tears

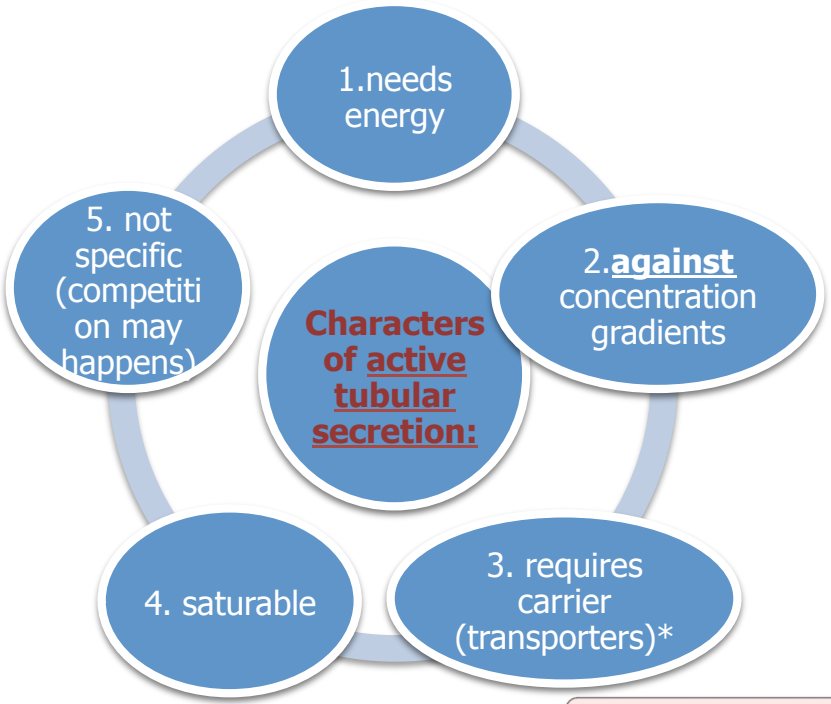
Principle processes of excretion

1. Glomerular filtration.
2. Active tubular secretion.
3. Passive or active tubular re-absorption

1. Glomerular Filtration

Where it occurs	Blood is filtered across a semi-permeable membrane into the Bowman's Capsule.
What does not get filtered	Blood cells, platelets, and plasma proteins are retained in the blood and not filtered.
Glomerular filtration of drugs occurs to	- Low molecular weight drugs. - Water soluble drugs. - Free form of the drugs (not bound to plasma proteins). - Drugs with low volume of distribution (Vd).

Glomerular Filtration Rate	
Definition	The amount of blood filtered by the glomeruli in a given time. Normal GFR = 125 ml/min. Depends on hydrostatic pressure of blood flowing in the capillaries.
Used for	GFR is used as a marker or indicator for kidney function.
Determined by	GFR is determined by creatinine, inulin (inulin is easily filtered by the kidney and not reabsorbed).



2- Active Tubular Secretion of Drugs

- Occurs mainly in proximal tubules.
- It increases drug concentration in filtrate.
-It is carrier mediated and saturable
Requires energy to transport drugs against Concentration gradients.
-Drugs undergo active secretion have excretion rate values greater than normal GFR.
- Secretion of ionized drugs into the lumen

e.g. penicillin

Types of transporters

- I. Transporters for organic acids — e.g Penicillin, aspirin, sulfonamides, Probenecid, uric acid
- II. Transporters for organic bases — e.g morphine, catecholamines, atropine, quinine

* Two drugs can compete for the same carrier: e.g Probenecid & penicillin (for organic acid carrier), & Probenecid & nitrofurant (for organic acid carrier)

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.

Competitive Active Tubular Secretion Of Drugs

Beneficial competition	Harmful competition
Probenecid & penicillin	Probenecid & nitrofurantoin
Probenecid competes with or retards renal tubular secretion of penicillin and thus less amount of penicillin will be excreted → increased duration of action of penicillin & its antibacterial action	Probenecid inhibits renal tubular secretion of nitrofurantoin thus decreases nitrofurantoin efficacy in urinary tract infections

3. Passive or active tubular re-absorption:

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

It takes place all along the renal tubules, and it increases half life of a drug.

	Passive Tubular re-absorption		Active tubular re-absorption
Location	In distal convoluted tubules & collecting ducts.		Mainly in proximal tubules
Function	Non-ionized drugs	undergo passive tubular re-absorption from tubular lumen back into blood (not excreted in the urine, urinary excretion will be low).	- It increases half-life of a drug. - It occurs with endogenous substances e.g. glucose, amino acids, electrolytes, uric acid, vitamins.
	Ionized drugs	are poorly reabsorbed, excreted easily in the urine, and urinary excretion will be high.	
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

Factor	Effect	Example
1. Renal blood flow	- Adequate renal function depends upon renal blood flow (Important for drugs excreted by glomerular filtration). - 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.
2. Molecular weight of the drug	Larger MW drugs are difficult to be excreted than smaller MW especially by glomerular filtration.	
3. Lipid solubility of drugs	Urinary excretion is inversely related to lipophilicity. Increased lipid solubility increases volume of distribution of drug and decreases renal excretion.	
4. 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.	**Aminoglycosides** **Tubocurarine**

Factors affecting renal excretion of drugs

Factor	Effect
5. Volume of distribution (Vd)	• 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 excretion rates.
6. 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.
7. Biological factors: (age)	• 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:

They have more total body water than adults, thus greater Vd 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 newborns.
⇓ glomerular filtration of drugs.

Effects of aging on the kidney (in elderly):

⇓ kidney size
⇓ renal blood flow
⇓ number of functional nephrons.
⇓ tubular secretion
Result:
⇓ GFR
⇓ drug clearance.

Factors affecting renal excretion of drugs

Factor	Effect	Example
8. Diseases states	Impair the elimination of drugs thus may increase half-life (t ½) of drugs. This may occur due to: 1- Reduced renal blood flow: Congestive heart failure Hemorrhage Cardiogenic shock 2- Decreased renal excretion: Renal disease (e.g. glomerulonephritis).	
9. pH of urine	- Normal urine (pH 5.3) is slightly acidic and favors excretion of basic drugs. So, most of acidic drugs will be reabsorbed back to the body. - Change pH of urine can inhibit or enhance the passive tubular re-absorption of drugs. **Ion trapping:** 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).	**Barbiturate**: weak acidic drug. **Amphetamine**: basic drug. **Aspirin**: acidic drug.

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.

Drugs excreted mainly by the kidney include:

- **Antibiotics:**
  - Penicillins, Cephalosporins
  - Aminoglycosides (Gentamycin)
  - Sulfonamides
- **NSAIDs**
- **Lithium**
- **Digoxin**
- **Immunosuppressants** (Cyclosporine)
- **Anticancer drugs** (Cisplatin)
- **Imipinem**

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

Dose adjustment in renal impairment

	Required	Not required
Dose adjustment	• Dose reduction of drugs is required when creatinine clearance is below 60 ml/min. • Monitor blood levels of drugs therapeutic drug monitoring.	When the drug taken is excreted mainly into feces biliary excretion.
Example	- 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, lithium, warfarin**)	**Ceftriaxone** **Doxycycline**

SUMMARY

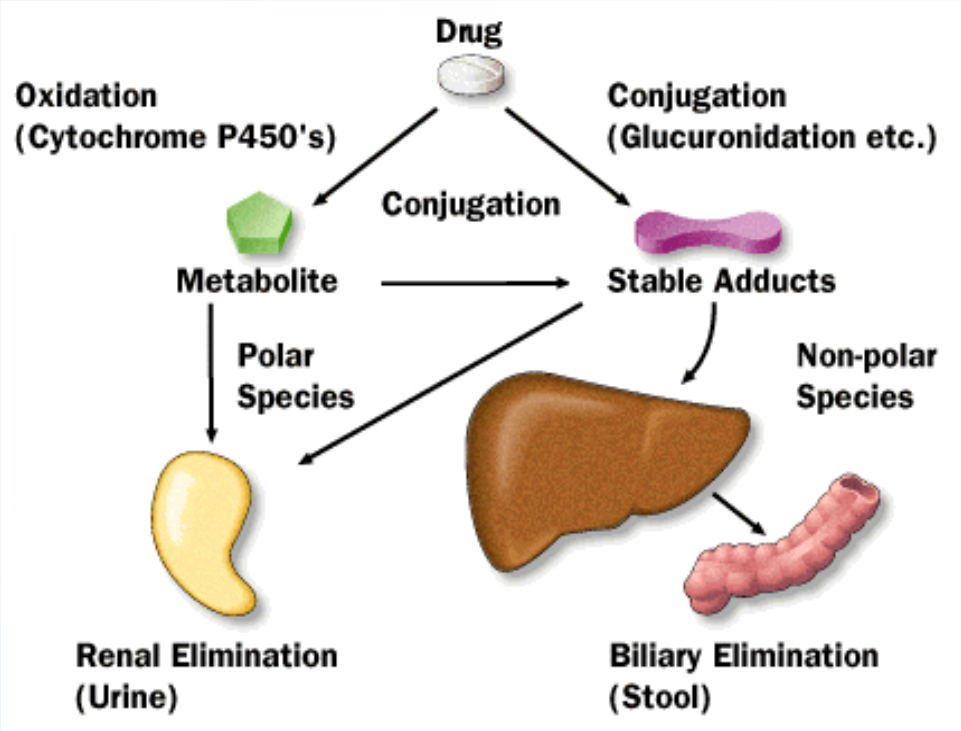
Identify main and minor routes of Excretion including renal elimination and biliary excretion?

Main:

1. Kidneys renal elimination = urine (Primary organ for drugs removal)
2. Biliary elimination = stool (Depends on the activity of hepatocytes)

Minor:

Pulmonary, Salivary, Mammary (Milk), and Skin.



Describe its consequences on duration of drugs.

○ **Glomerular filtration**:

Drugs that bound to plasma proteins have longer duration than those found freely in the plasma (*low volume of distribution= easily filtered*)

○ **Active tubular secretion**:

- Needs energy
- Requires carriers (unspecific ones = *competition* may happen).
- When two drugs compete for the same carrier, one of them will be excreted, while the other will stay in the blood (*=increase half-life*)

occurs mainly in proximal tubules

○ **Passive or active tubular re-absorption**:

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

Polar drugs: are readily excreted in urine and poorly reabsorbed.

Acidic drugs: are best excreted in alkaline urine (Urine alkalization by: *sodium bicarbonate*).

Basic drugs: are best excreted in acidic urine (Urine acidification by: *ammonium chloride*).

Lipid soluble drugs: are reabsorbed back and excretion will be low.

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

MCQs

1-Which of the following is a minor route of excretion:
A-Pulmonary excretion
B-Salivary excretion
C-Both A&B
D-Biliary excretion

2-Which of the following if filtered through the glomeruli:
A-Blood cells
B-Plasma proteins
C-Platelets
D-None of the above

3-Glomerular filtration of drugs occurs to :
A-Water soluble drugs
B-Drugs with low volume of distribution
C-Free form of drugs
D-All of the above

4-Passive tubular reabsorption of drugs occurs in:
A-Proximal convoluted tubules
B-Collecting ducts
C-Distal convoluted tubules
D-Both B&C

5-Increase ionization of drug means:
A-Increase its water solubility
B-Drecrease its water solubility
C-Increase its lipid solubility
D-None of the above

1-C 2-D 3-D 4-D 5-A 6-C 7-A 8-D 9-D 10-C 11-A

6-Most drugs are:
A-Weak acids
B-Weak bases
C-Both A&B
D-None of the above

7-Normal urine favors excretion of:
A-Basic drugs
B-Acidic drugs
C-Both acidic and basic drugs
D-Neither basic nor acidic

8-which of the following is a chractaristic of creatinine:
A-Produced from muscles
B-Freely filtered
C-Lipid soluble
D-Both A&B

9-Drugs excreted mainly by the kidney include:
A-NSAIDs
B-Lithium
C-Digoxin
D-All of the above

10-Which of the following is used to assess renal function:
A-Inulin
B-Creatinine
C-Both A&B
D-None of the above

11-Salfonamides are examples of which of the following:
A-Antibiotics
B-NSAIDs
C-Immunosuppressants
D-Anticancer drugs

PHARMACOLOGY 433

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We hope that we made this lecture easier for you

Good Luck !