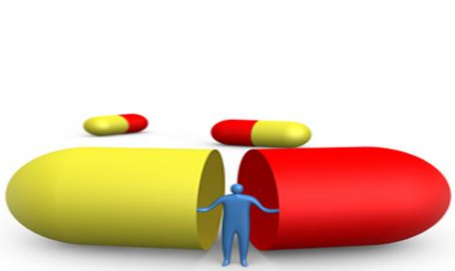


Pharmacology Team

Renal Excretion of Drugs

Done by: Ahlam Almutairi

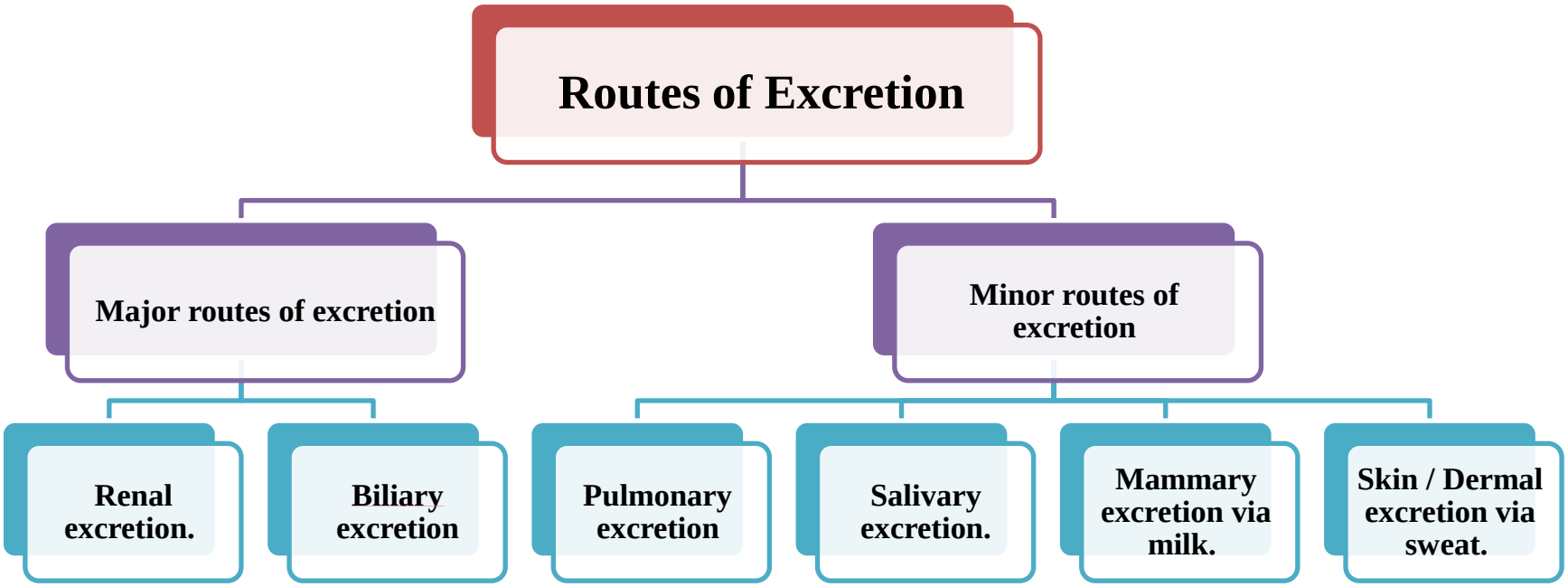
Reviewed by : Ali Alfraidi

Red	**Important**
Purple	Extra Notes
Orange	To differentiate
Black	From the slides
Blue	similar

OBJECTIVES

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

- **Identify main and minor routes of Excretion including renal elimination and biliary excretion**
- **Describe its consequences on duration 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.**



*The most important organ for drug excretion is the kidney

Structure of kidney

The structural unit of kidney is NEPHRON

That consists of :

- **Glomerulus**
- **Proximal convoluted tubules**
- **Henle's loop (Ascending –Descending)**
- **Distal convoluted tubules**
- **Collecting ducts**

Normal kidney functions

- Regulation of NaCl and electrolyte content (aldosterone, natriuretic peptides)
- Regulation of water balance (anti-diuretic hormone)
- Excretion of wastes, drugs, drug metabolites such as
  - Urea
  - Uric acid
  - Creatinine

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

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**.(present of RBC and protein indecates abnormal filtiration)

-Most drugs are filtered through glomerulus.

Glomerular filtration of drugs occurs to:

-Low molecular weight drugs

-Water soluble drugs (polar, Ionized) e.g aminoglycosides, tubocurarine*

-Free form of the drugs (not bound to plasma proteins).

-Drugs with low volume of distribution (Vd) (most of the drug is restricted into the blood circulation so it's easy to go to the kidney for filtration)

*tubocurarine is a skeletal muscle relaxant= polar = not given orally

ACTIVE TUBULAR SECRETION

(Active= needs Energy)

-occurs mainly in proximal tubules

-It increases drug concentration in filtrate

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

-Secretion of ionized drugs into the lumen (later it will form the urin)

e.g. penicillin

Characters of active tubular secretion:-

-Is an active process. -needs energy

-transport drugs **against** concentration gradients

-requires carriers (**transporters**)

-Saturable

-Not specific (because there is no specific carrier for each drug but there are carriers for a collection of drugs)

(**competition** may happens)

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 clearance 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

TUBULAR RE-ABSORPTION OF DRUGS

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

-It takes place all along the renal tubules.

-Drugs undergo tubular re-absorption have excretion rates less than the GFR.

Re-absorption increases half life of a drug.

Re-absorption may be passive or active.

Passive Tubular re-absorption of drugs

-In distal convoluted tubules & collecting ducts.

-Only lipid soluble drugs (non-ionized) undergo passive tubular re-absorption from tubular lumen back into systemic circulation (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.

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

GLOMERULAR FILTRATION RATE

GFR=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. (if there is decline of GFR indicate a problem ,so most of the drugs will be retained in the body and not going to be filtered)

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

ACTIVE TUBULAR SECRETION

Types of transporte:

Transporters for organic acids

e.g -Penicillin ,aspirin (salicylates), sulfonamides, uric acid (endogenous), Probenecid.

Transporters for organic bases

e.g -morphine, catecholamines, atropine, quinine, neostigmine.

Competitive active tubular secretion of drugs

Beneficial competition:

Probenecid & penicillin

Probenecid inhibits renal tubular secretion of some **acidic drugs (e.g. penicillin)** and thus prolong duration of action of penicillin & its antibacterial action.

Harmful competition:

Probenecid & nitrofurantoin

Probenecid inhibits renal tubular secretion of **nitrofurantoin** thus decreases its efficacy in urinary tract infections.

(nitrofurantoin it's not going to produce its action)

TUBULAR RE-ABSORPTION OF DRUGS

Active tubular re-absorption of drugs

-It increases half-life of a drug.

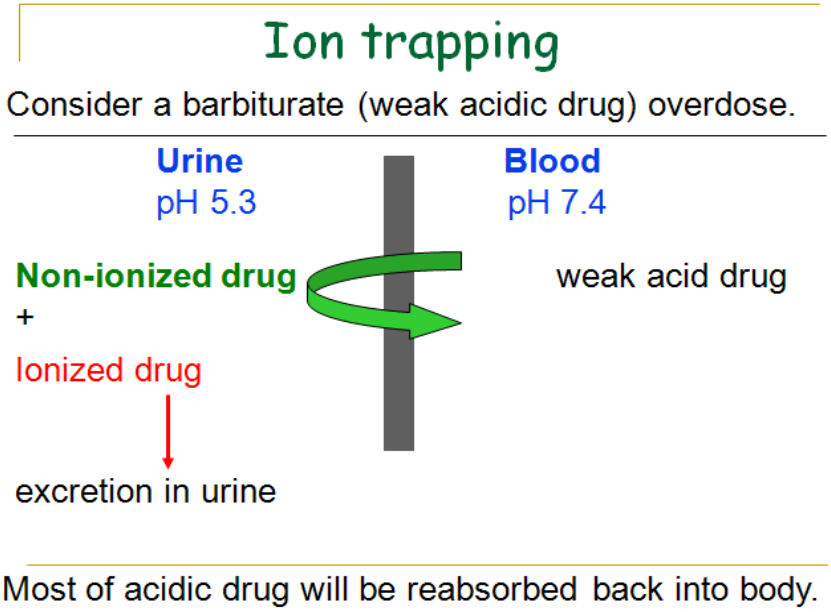
-It occurs with endogenous substances or nutrients that the body needs to maintain e.g. glucose, amino acids, electrolytes, uric acid, vitamins.

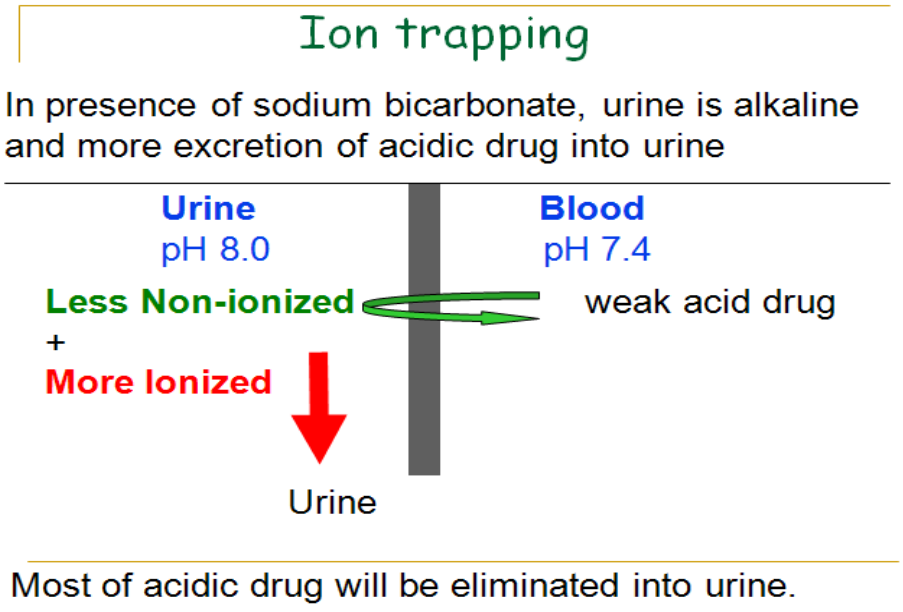
Probenecid acts as a uricosuric agent in treatment of gout.

by inhibiting active tubular re-absorption of the endogenous metabolite uric acid.

Urinary pH trapping (Ion trapping)

- Most drugs are weak acids or weak bases thus by changing pH of urine can inhibit or enhance the passive tubular re-absorption of drugs.
- Normal urine (pH 5.3) slightly acidic and favors excretion of basic drugs.
- 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).





Factors affecting renal excretion of drugs

Blood flow to the kidney

increased perfusion leads to increased excretion; Important for drugs excreted by glomerular filtration. •

Physiochemical properties of drugs

Drug MW: larger MW drugs are difficult to be excreted than smaller MW especially by glomerular filtration. •

Drug lipid solubility: increased lipid solubility increase volume of distribution of drug and decrease renal excretion. •

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

Binding characteristics of the drugs •

Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus. **Only** • unbound or free drug appear in glomerular filtrate. Protein bound drug has long half lives.

Degree of ionization •

Urine pH

Biological factor e.g. age

Age can affect renal clearance. Renal clearance is reduced in neonates and elderly. •

Disease states

impairs the elimination of drugs e.g. congestive heart failure, pyelonephritis•

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.
- **Dose reduction** is advisable otherwise toxicity may occur.

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 that can decrease renal clearance

This may increase half-life (t ½) of drugs

- ❑ Reduced renal blood flow (Congestive heart failure., Hemorrhage, Cardiogenic shock)
- ❑ Decreased renal excretion : Renal disease (e.g. glomerulonephritis).

Renal clearance of drugs

$$CL_r = (C_u V_u)/Cp$$

Cu : concentration in the urine

Vu : volume of urine

Cp: plasma concentration

- Creatinine clearance (CrCl) is used to estimate glomerular filtration rate.

Creatinine clearance and drugs excretion

- ❑ Creatinine clearance rate (CrCl) is the volume of blood that is cleared of creatinine per unit time.
- ❑ CrCl is a useful measure for GFR because creatinine is produced from muscle and freely filtered (low MW, water soluble, and is not protein bound).

The Cockcroft-Gault equation for estimation of creatinine clearance

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

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

*GFR is more accurate than CL for **Glomerular function**

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 (mainly = more than 60% excreted by kidney)
  - Have narrow therapeutic index (e.g. lithium, digoxin, warfarin).

Drugs excreted mainly by the kidney include

-Antibiotics:

- ❑ Penicillins, cephalosporins ,Aminoglycosides (gentamycin), Sulfonamides

-Non steroidal anti-inflammatory drugs (NSAIDs)

-Lithium

-**Digoxin**

-Immunosuppressants (cyclosporine)

- **Anticancer drugs** (cisplatin)

These drugs are contraindicated in: Renal failure – 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).

When dose reduction is not required in renal impairment ?

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

Summary

- **Competition for active secretion prolongs half life of some drugs e.g penicillin and probenicid**
- **Protein binding of drugs inhibits renal excretion of drugs except those that are actively secreted.**
- **NSAIDS e.g aspirin and ibuprofen inhibits the production of PGs and therefore reduces renal perfusion and GFR.**
- **Irrespective of the mechanism of renal excretion of drugs, decreased renal blood flow decrease excretion of drugs.**

Questions

1-Which one of the following drugs, is an acidic one:
A-Amphetamine
B-Gentamicin
C-Aspirin

2- An old patient comes to you with bacterial infection, fever and history of renal impairment, Which one of the following drugs would you prefer describing:
A- Penicillin
B- Ceftriaxone
C- Aminoglycosides

3-Dose reduction of drugs is required to prevent toxicity especially with a narrow therapeutic index drugs.which one of the following drugs we've to
prolong its dosing intervals without decreasing the dose to prevent toxicity :
A- Digoxin
B- haemovillin
C-Gentamicin

4- The effect of probanacid on penicillin is :

A- decrease the concentration of Penicillin in the plasma

B- No effect on Penicillin

C- Increase the concentration of Penicillin in the plasma

Answers:

1- C

2- B

3- C

4- C