

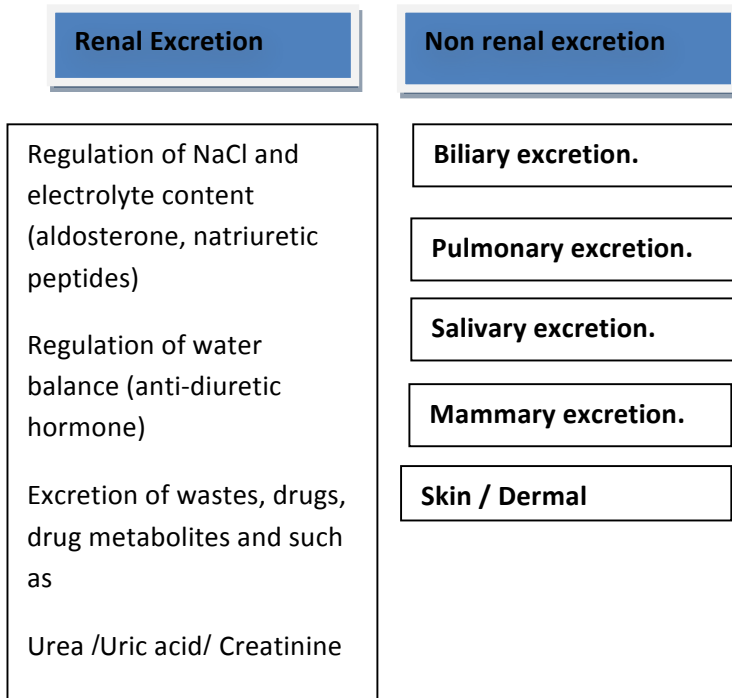
Medical

Background

Renal Excretion of Drugs

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Routes of Excretion



Renal Excretion of drugs

The most important organ for drug excretion is the kidney.

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

Glomerular filtration.

Active tubular secretion.

Passive or active tubular re-absorption.

Glomerular filtration (GF)

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

Hydrostatic pressure pushes a portion of blood to be filtered across a **semi-permeable membrane into the Bowman's Capsule.**

Most drugs are filtered through glomerulus.

Blood cells, platelets, and plasma proteins are retained in the blood and not filtered.

Glomerular Filtration Rate (GFR)

The amount of blood filtered by the glomeruli in a given time (GFR = 120-130 ml/min).

Glomerular filtration occurs to:

Low molecular weight drugs

free form of the drugs (not bound to plasma proteins). = if it's bound it will not filtrate

Water soluble drugs e.g. aminoglycosides, tubocurarine = ionized form

Drugs with **low volume of distribution** (Vd) = if it is low distribution the mean the concentration of drug in circulation more than tissue ,so it will filtrate rapidly

GFR is **determined by creatinine, inulin** (inulin is easily

filtered by kidney not reabsorbed) = like what we have been taken in physiology 😊

Active Tubular Secretion of drugs

occurs mainly in **proximal tubules**

It **increases drug concentration** in filtrate

Drugs undergo active secretion have excretion rate values greater than normal GFR = any drug its excretion more than 120-130 the mean the proximal tubule will secrete the drug also which is called "active secretion"

Secretion of K⁺, H⁺, ammonia; excess amino acids

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

Characters of active tubular secretion:

Is an active process

Not specific (competition may happens)

needs energy = need ATP

Saturable = which is mean if there are 10 carrier it will just transport 10 molecules of the drug then become saturation

requires carriers (transporters)

can transport drugs against concentration gradients

Two secretion mechanisms are identified

System for secretion of organic acids/anions

- Penicillin, salicylates,(aspirin) sulfonamides
- Probenecid, uric acid

System for organic bases / cations

- Atropine, morphine
- Catecholamines, quinine, neostigmine

Active tubular secretion of drugs

Therapeutic advantages of competition:
Probenecid is used to block renal tubular secretion of some acidic drugs (e.g. penicillin) and thus prolong its duration.

Therapeutic disadvantages of competition:

probenecid inhibits renal tubular secretion of nitrofurantoin thus decreases its efficacy in urinary tract infections (UTIs).=because nitrofurantoin act of urinary tract ,so it's must be secretion by proximal tubule to act in its site.

Tubular re-absorption

- After glomerular filtration, drugs may be reabsorbed from tubular lumen into systemic circulation.= if it's still lipid soluble
- It takes place all along the renal tubules.
- Drugs undergo tubular re-absorption have excretion rates less than the GFR. e.g. Glucose
- Re-absorption increases half life of a drug.
- Re-absorption may be active or passive.

Passive Tubular re-absorption

- In distal convoluted tubules & collecting ducts.
- Only lipid soluble drug undergoes passive tubular re-absorption from tubular lumen into systemic circulation.
- Lipophilic drugs can be passively reabsorbed back (urinary excretion will be low).
- Ionized drugs (water soluble) are poorly reabsorbed & so urinary excretion will be high.

Active tubular re-absorption

- It occurs with endogenous substances or nutrients that the body needs to conserve. e.g. glucose, electrolytes, amino acids, uric acid, vitamins.
- Probenecid acts as a uricosuric agent in treatment of gout.
- It increases excretion of uric acid in urine by inhibiting active tubular re-absorption of the endogenous metabolite uric acid.

Passive Tubular re-absorption and urinary pH trapping (Ion trapping)

- Most drugs are weak acids or weak bases thus by changing pH of urine via chemicals can inhibit the passive tubular re-absorption of drugs.
- Urine is normally slightly acidic and favors excretion of basic drugs.

Generally basic drugs will excrete with acidic urine

And acidic drugs will excrete with basic urine

Urinary pH trapping

- It is used to enhance renal clearance of drugs during toxicity.
- Urine acidification: by ammonium chloride (NH_4Cl) increases excretion of basic drugs (amphetamine, gentamicin).
- Urine alkalization: by sodium bicarbonate (NaHCO_3) increases excretion of acidic drugs (aspirin, barbiturates).

Ion trapping

In presence of sodium bicarbonate, urine is alkaline and more excretion of acidic drug into urine

Most of acidic drug will be eliminated into urine.

If the drug is basic and the urine is basic, too then most of the drug will become non-ionized and reabsorbing into blood.

In presence of sodium bicarbonate, urine is alkaline and more excretion of acidic drug into urine

Most of acidic drug will be eliminated into urine.

If the drugs acid and the urine is basic the drug will eliminated into urine .

Factors affecting renal excretion of drug

Physiochemical properties of drugs

Molecular weight

Lipid solubility

Volume of distribution

Binding character

Degree of ionization

Blood flow to the kidney

Urine pH

Biological factor e.g. age

Disease states

Factors affecting renal excretion

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

Drug lipid solubility: urinary excretion is inversely related to lipophilicity, increased lipid solubility increase volume of distribution of drug and decrease renal excretion.

Volume of distribution: 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.

Renal blood flow: increased perfusion leads to increased excretion; Important for drugs excreted by glomerular filtration.

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.

Biological factor: Age can affect renal clearance. Renal clearance is reduced in neonates and elderly.

Disease states impairs the elimination of drugs e.g. hypertension, Diabetes, pyelonephritis

Drug renal clearance:

a rate of excretion of a drug by the kidney into urine relative to the plasma drug concentration.

$$\text{Renal Clearance} = \frac{\text{Excretion rate (mg/min)}}{\text{Plasma concentration (mg/ml)}} \text{ (ml/min)}$$

Not important in our exam the equation not included 😊

- Renal clearance of many drugs and their metabolites depends on adequate renal function.

Drug renal clearance:

- If renal clearance is impaired, this may increase $t_{1/2}$ of drugs and toxic levels of drugs may remain in the body.
- Renal clearance is especially important for some drugs which are:
 - Mainly excreted by the kidney
 - Have narrow therapeutic index (e.g. lithium, digoxin, warfarin).

Diseases that can decrease renal clearance

Reduced renal blood flow

1-Congestive heart failure.

2- Hemorrhage

3-Cardiogenic shock

Decreased renal excretion :

-Renal disease (e.g. glomerulonephritis).

This may increase half-life ($t_{1/2}$) of drugs

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)=increase the interval for example IF we give him the drug twice a day we will give it to him just once a day

-decrease the dose without changing dosing intervals (e.g. digoxin)

Monitor blood levels of drugs (therapeutic drug monitoring).

Dose reduction in renal impairment

Antibiotics:

Penicillins, cephalosporins (Except **Ceftriaxone** which is excreted through the bile into the feces and, therefore, is frequently employed in patient with renal insufficiency Pharmacology Lippincott P.366)

Aminoglycosides (gentamycin)

Sulfonamides

Non steroidal anti-inflammatory drugs (NSAIDs)

Lithium

Digoxin

Immunosuppressants (cyclosporine)

Anticancer drugs (cisplatin - cyclophosphamide)

These drugs are contraindicated in:

Renal failure – Elderly patients= because their kidney already weak ☹️

When dose reduction is not required in renal impairment ?

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

Creatinine clearance and drugs excretion

Creatinine clearance rate (CCr or CrCl) is the volume of blood that is cleared of creatinine per unit time.

CrCl is a useful measure for approximating the GFR because creatinine is produced from muscle and freely filtered (**low MW(molecular weight), water soluble, and is not protein bound**).

Drugs that are primarily excreted by the kidney

(> 60%) needs dose adjustment.

Estimation of Creatinine Clearance

The Cockcroft-Gault equation for creatinine clearance estimation

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

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

Equation not included in our exam ☺️ and we already took them in biochem.

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- Aminoglycosides

C- Ceftriaxone

3- Dose reduction of drugs is required to prevent toxicity especially with a narrow therapeutic index drugs. Depending with this statement, which one of the following drugs we've to prolong its dosing intervals without decreasing the dose to prevent toxication:

A- Digoxin

B- haemovillin

C- Gentamicin

4- If you've a patient who is taken amphetamine, which one of the following used to enhance the drug excretion:

A-Calcium carbonate

B-Sodium hydroxide

C-Ammonium chloride

Answers: 1- C , 2- C , 3- C , 4- C