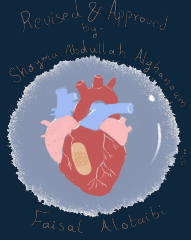


PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Renal Excretion Of Drugs

Objectives:

- Identify main and minor routes of Excretion including renal elimination and biliary excretion
- Describe its consequences on duration of drugs
- Identify the different factors controlling renal excretion of drugs
- Know the meaning of urinary ion trapping
- Know how we can prescribe drugs in patients with renal impairment

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

Notes

helpful video

Editing file

Routes of Excretion

Major routes of excretion

- Renal excretion
- Biliary excretion

Minor routes of excretion

- Pulmonary excretion (exhalation)
- Salivary excretion
- Mammary excretion via milk
- Skin / Dermal excretion via sweat
- tears

Structure of kidney

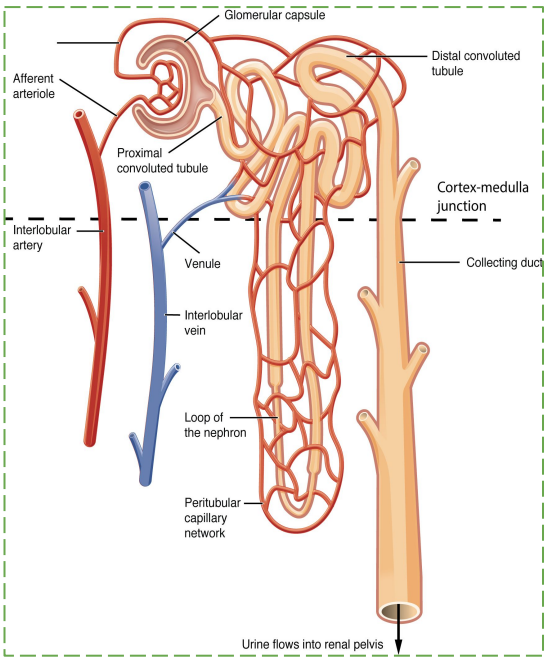
The structural unit of kidney is NEPHRON that consists of :

Glomerulus → Proximal Convoluted tubules → Henle's loop (Ascending-Descending) → Distal Convoluted tubules → Collecting ducts

Normal kidney functions:

Females slides only

1. Regulation of electrolytes (aldosterone)
2. Regulation of water balance (anti-diuretic hormone)
3. Excretion of wastes & drug metabolites such as (Urea ,Uric acid ,Creatinine)
4. The most important organ for drug excretion is the kidney.



Renal excretion:

Urinary excretion of drugs occurs through three processes:

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

1- Glomerular filtration (GF):

- Depends upon renal blood flow (Normal GFR = 125-130 ml/min)
- Most drugs are filtered through glomerulus.
- Blood is filtered across a semi-permeable membrane into the Bowman's Capsule.
- Filtrate contains water, glucose, amino acids, sodium bicarbonates, organic solutes and electrolytes (sodium, potassium, chloride).
- Blood cells, platelets, and plasma proteins are retained in the blood and **not filtered.**
  In healthy person's urine contains very little protein . If the protein is high that mean have Proteinuria (excess proteins in the urine)
- Driving force for GF is hydrostatic pressure of blood flowing in capillaries.

Glomerular filtration Rate (GFR): every point here is from girls slides except the last one

- 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.
- Creatinine clearance (CrCl) is used as a marker instead of GFR.
- GFR is determined by creatinine, inulin (inulin is easily filtered by kidney not reabsorbed).

Glomerular filtration of drug occurs to:

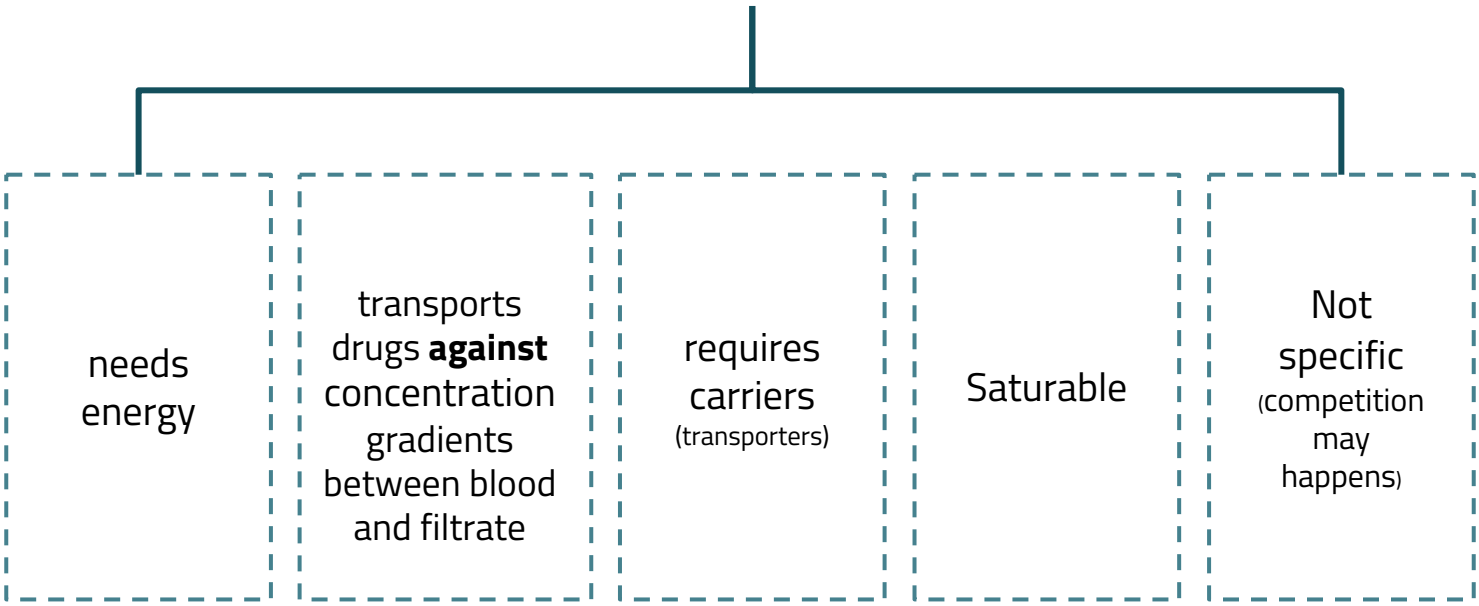
1	Low molecular weight drugs (most proteins have high MW and are not filtered)
2	Polar or ionized Water soluble drugs e.g. aminoglycosides,tubocurarine
3	Free form of the drugs (not bound to plasma proteins) Bound proteins >>>trapped in the blood >>> can not be filter because high MW
4	Drugs with low volume of distribution (Vd) If the drugs have low VD that mean have low conc.in tissue and high conc. on blood

Which of the following will be filter easily ? the answer will be 1,2,3,4

2-Active Tubular Secretion of Drugs :

- occurs mainly in proximal tubules
- It increases drug concentration in the filtrate.because the drug will be secreted from the blood to the filtrate
- Drugs undergo active secretion have excretion rate values greater than normal GFR.
- Secretion of ionized (water soluble) drugs into the lumen e.g. penicillin G

Characters of active tubular secretion:



we don't have specific carriers for each type of drug, we only have acidic carriers and basic carriers and a competition may happen if 2 acidic or 2 basic drugs were taken at the same time

Types of transporters

for organic acids

Penicillin, aspirin, uric acid, sulfonamides, probenecid

probenecid can inhibits active tubular secretion of acidic drugs

for organic base

morph**ine**, catecholam**ines**, atrop**ine**, quin**ine**

(ine) basic drugs

وإلى حدٍ ما

lipid soluble

Competitive active tubular secretion of drugs:

Female slides only

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.

Two drugs can compete for the same carrier:

● Probenecid & penicillin ● Probenecid & nitrofurantoin

Beneficial competition

Probenecid & penicillin G

● Both require the same carrier for renal excretion

● Probenecid competes with or retards renal tubular secretion of penicillin G and thus less amount of penicillin G will be excreted → prolonged duration of action(by 2 folds) of penicillin G & increase in its **antibacterial action**

Harmful competition

Probenecid & nitrofurantoin

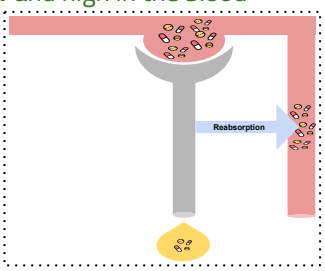
● Probenecid inhibits renal tubular secretion of nitrofurantoin
→ decreases its efficacy in urinary tract infections (UTIs)

nitrofurantoin's site of action is in the lumen to treat UTI, probenecid will inhibit the secretion of nitrofurantoin therefore decreases its efficacy

3-Tubular reabsorption of drugs:

Females slides only

- It takes place along all the renal tubules.
- After glomerular filtration, drugs may be reabsorbed back from tubular lumen into systemic blood circulation. So the concentration of the drug in the urine will be low and high in the blood
- Reabsorption increases half life of a drug
- Reabsorption may be passive or active



Passive Tubular reabsorption of drugs

1- In distal convoluted tubules & collecting ducts.

2- Only lipid soluble drugs (non-ionized) undergo passive tubular re-absorption from tubular lumen back into blood (not excreted in the urine, urinary excretion will be low).

3- Ionized drugs (water soluble) are poorly reabsorbed, excreted easily in the urine, and urinary excretion will be high.

Active Tubular reabsorption of drugs

1-It occurs with endogenous substances or nutrients that the body needs to conserve against the gradient **e.g:** glucose, electrolytes, amino acids, uric acid, vitamins.The examples are not important

2- Probenecid inhibits active tubular re-absorption of uric acid So, It increases excretion of uric acid in urine.

3- Probenecid acts as a uricosuric agent in the treatment of gout.

Factors affecting renal excretion of drugs:

1-Blood flow to the kidney

- 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. PG : A2,I2 have important function>>1-maintain normal renal blood flow by vasodilation 2- protection of stomach
- Irrespective of the mechanism of excretion, Increased perfusion leads to increased contact of drug with secretary site and thus increased excretion.
- Important for drugs excreted by Glomerular filtration

2-Physicochemical properties of drugs

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 (Vd) 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 (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 renal excretion rates.
Plasma protein binding :	➢ 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. ➢ The renal clearance of drugs which are extensively bound to plasma proteins is increased after displacement with another drugs. E.g. Gentamicin-induced nephrotoxicity by Furosemide (Furosemide displaces gentamicin from protein)

Cont...

Factors affecting renal excretion of drugs:

3-Biological factor *only in girls slide

- 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.

4-Disease states

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Impairs 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)

5-Urine PH:

Urine pH varies from 4.5 to 8 depending upon the diet e.g. meat causes more acidic urine and carbohydrates rich food may increase urinary pH

6-Plasma concentration

Glomerular filtration and reabsorption are directly affected by plasma concentration of drug.

Renal excretion of drugs and pH of urine

1. Most drugs are weak acids or weak bases
2. Normal urine (pH 5.3) slightly **acidic** and favors excretion of **basic drugs.** Basic drug +acidic urine = ionized >>easily to excecreat
3. Most of acidic drugs will be reabsorbed back into body.
   Acidic drug +acidic urine = ionized >>hard to excecreat
4. Changing the pH of urine can inhibit or enhance the passive tubular re-absorption of drugs.
5. Urine pH varies from 4.5 to 8 depending upon the diet e.g. meat decreases urinary pH (more acidic urine) and carbohydrates rich food may increase urinary pH.

Urinary pH trapping (Ion trapping)

It is used to enhance renal clearance of drugs during toxicity

Urine acidification	**Urine alkalization**
By ammonium chloride (NH_4Cl) increases excretion of basic drugs : amphetamine, gentamicin Basic drugs favors acidic urine	By sodium bicarbonate ($NaHCO_3$) increases excretion of acidic drugs: aspirin,barbiturates Acidic drugs favors basic urine

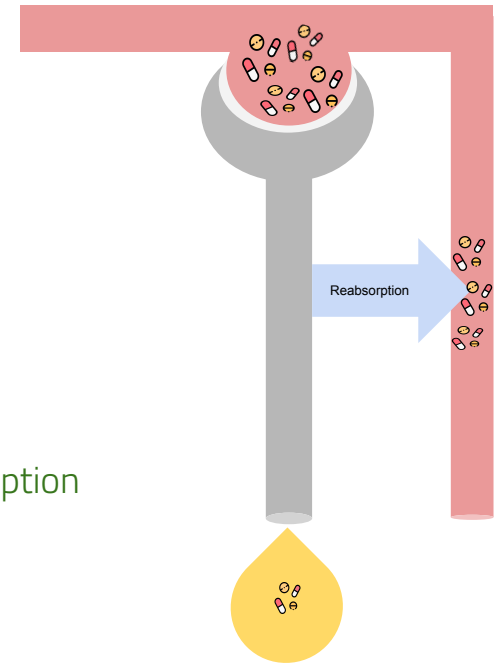
Cont...Urinary pH trapping (Ion trapping)

Example of urine alkalinisation:

1- Consider a barbiturate (weak acidic drug Ex: aspirin) overdose

Urine
pH 5.3 acid

Aspirin will be:
More non-ionized portion
+
Less ionized portion
لسى فيه lipid solubility >>>reabsorption



blood
pH 7.4

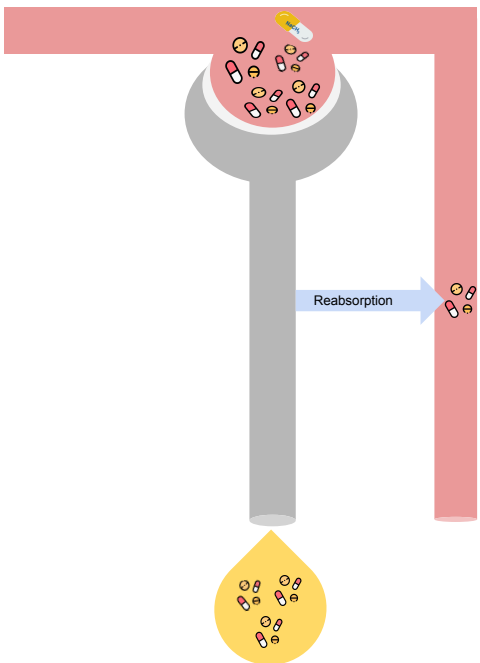
Weak acid drug

Most of acidic drug will be reabsorbed back into body

2- In presence of sodium bicarbonate, urine is alkaline and more excretion of acidic drug Ex: aspirin into urine.

Urine
pH 8 alkaline

Aspirin will be:
Less non-ionized portion
+
More ionized portion
Because of bicarbonate



blood
pH 7.4

Weak acid drug

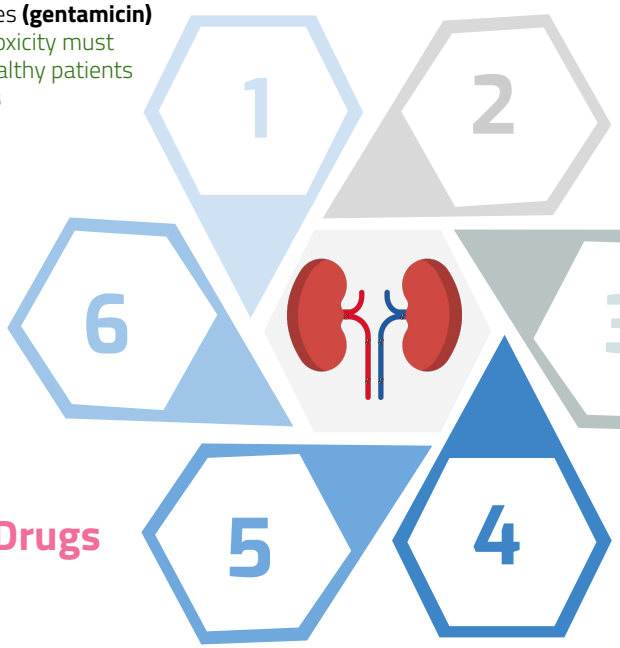
Most of acidic drug will be eliminated into alkaline urine

Notice that in (1) the urine PH still the same , so the excretion of barbiturate is low .
While in (2) after the addition of NaHCO3 the excretion of barbiturate is increased.

Drugs Excreted Mainly by The kidney:

Antibiotics

- Penicillins
- Aminoglycosides **(gentamicin)**
  Cause nephrotoxicity must describe for healthy patients
- Cephalosporins
- Sulfonamides
- Vancomycin
- Imipenem



NSAIDs

- Aspirin

Lithium

Digoxin

Anticancer Drugs

- Cisplatin

Immunosuppressants

- (cyclosporine)

➔ **Be careful upon prescribing those drugs , they may be contraindicated or need dose adjustment in:**

- Renal failure patients
- Elderly patients

Check physiology 3rd lecture	**Drug renal clearance**	**Creatinine clearance Rate (CrCl)**
Definition	is the unit volume (ml) of plasma cleared by the kidney per unit time (min)	
Importance	Depends on adequate renal function. • Important for drugs: ➔ With narrow therapeutic index e.g. lithium, digoxin, warfarin ➔ Excreted mainly by the kidney.	Used to estimate GFR WHY? ➔ Because it's produced from muscles and freely filtered.(low MW, water soluble, and is not protein bound).
Equation name		Cockcroft-Gault equation for estimation of creatinine clearance
Equation	$CLr = \frac{\text{Excretion rate}_{(mg/min)}\,[CuVu]}{\text{Plasma concentration}_{(mg/ml)}\,[Cp]}$ CLr: renal clearance (ml/min) Cu : drug concentration in the urine Vu : volume of urine in 24 hours Cp: drug concentration in the blood	For Female CrCl: $= \frac{\mathbf{0.85}(140-age)\,BW}{SCr \times 72}$ For Male CrCl: $= \frac{(140-age)\,BW}{SCr \times 72}$ SCr =serum creatinine BW=Body weight
Unit	**(ml/min)**	

Decreased renal clearance may occur in:

Yes this is repeat >> عشان اختلاف الترتيب **والتصنيف** بين سلايدات الأولاد والبنات

.

If renal clearance is impaired, this may increase t ½ of drugs and may result into drug toxicity.

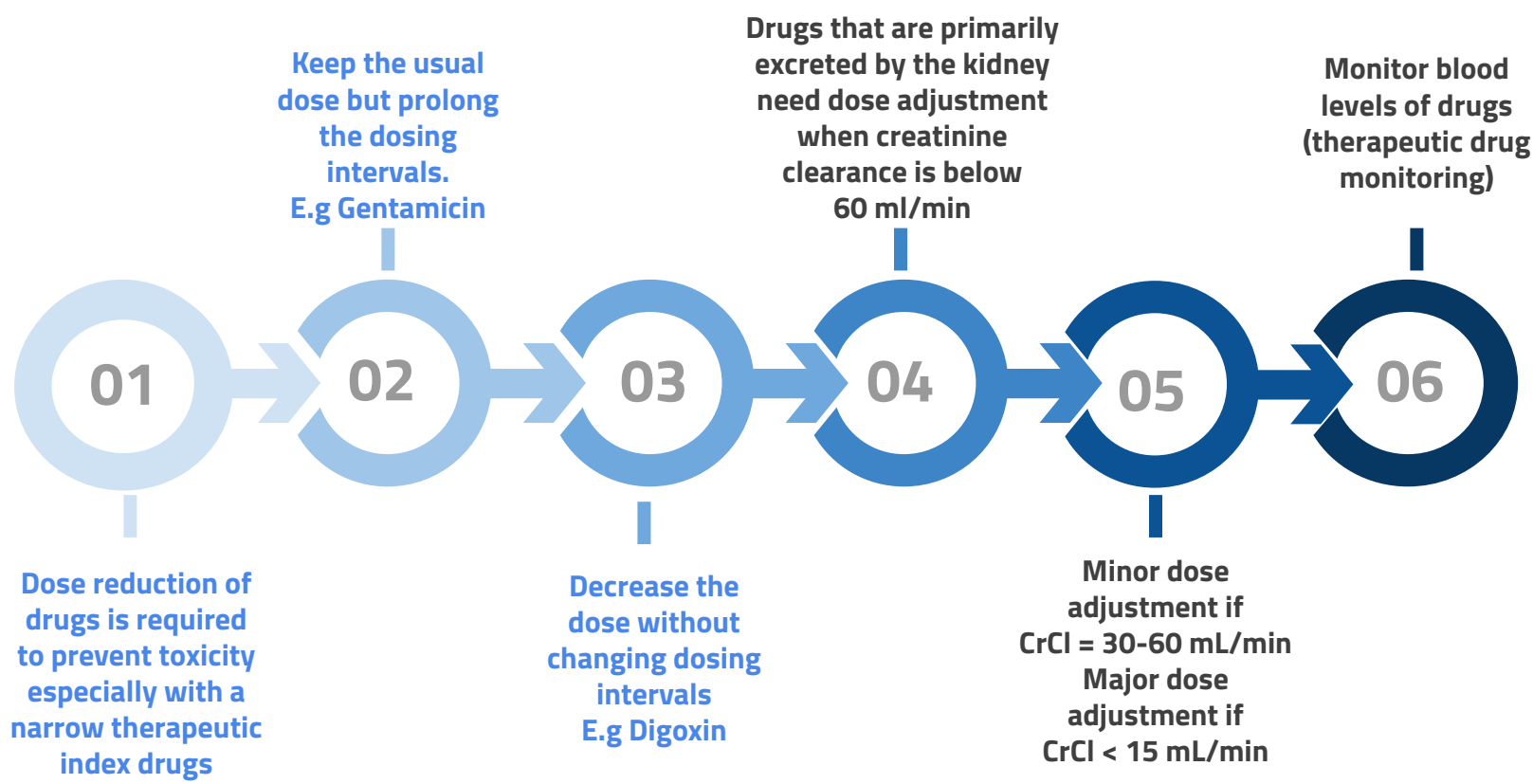
1-Reduced renal blood flow

- Congestive heart failure
- Hemorrhage
- Cardiogenic shock

2-Decreased renal excretion

- Renal disease (e.g. glomerulonephritis)

So what should we do in this situation ?



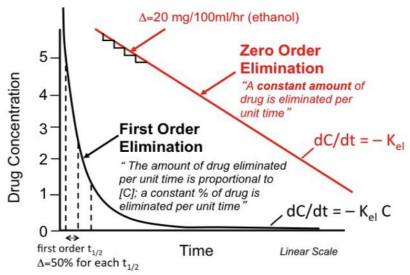
When does reduction is not required in renal impairment ?

➔ **Occurs to few drugs that are excreted mainly into feces (Biliary excretion)**
e.g. ceftriaxone and doxycycline doesn't need dose adjustment in renal impairment.

➔ **Some drugs undergo enterohepatic circulation back into systemic circulation**

Orders of Elimination:

	Zero-Order	First-Order
HALF-LIFE	Is NOT EQUAL at two places on the curve	Is EQUAL at two places on the curve
lost per unit time	Constant AMOUNT	Constant PERCENTAGE
The rate of excretion	is independent of the concentration of drugs in the plasma (constant amount is eliminated per unit time). the rate of elimination remains constant, even if the dosage is increased, this may cause toxicity.	is directly proportional with concentration of drug in plasma. (constant percentage is eliminated per unit time). if the dose is increased, the excretion rate is increased.
examples	Ethanol(alcohol) phenytoin aspirin	penicillin aminoglycoside quinolones



Q from Dr slides for the First order of elimination

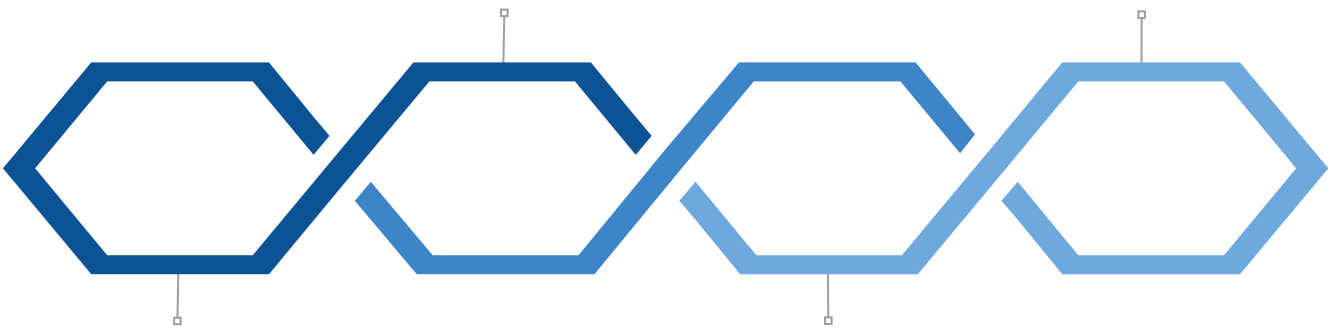
Q: If a drug with a 2-hour half life is given with an initial dose of 8 mcg/ml, assuming first-order kinetics, how much drug will be left at 6 hours?
A) 8 mcg\ml. B) 4 mcg\ml. C) 2 mcg\ml D) 1 mcg\ml

Answer : 50% is lost every 2h
First 2h : 8mg → 4mg.
Second 2h : 4mg →2mg.
Third 2h : 2mg → 1mg

Risk Factors for NSAIDs-Associated Acute Renal Failure:

PGI2 and PGE2 antagonize the local effects of circulating angiotensin II, endothelin,vasopressin, and catecholamines that reduce renal circulation

Prostaglandins preserve GFR by antagonizing arteriolar vasoconstriction.



Prostaglandins (PGs) have major role in the preservation of renal function when pathologic states compromise physiologic kidney processes.

A significant reduction in GFR can occur following administration of a NSAID to a patient with any underlying disease states (NSAIDs inhibit production of PGs)

Summary From the slides

- ★ 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).
- ★ Inulin and creatinine are used to assess renal function.
- ★ Competition for active secretion prolongs half life of some drugs e.g penicillin and probenecid.
- ★ Enterohepatic circulation prolongs half life of the drug.
- ★ 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.

MCQ

1-Glomerular filtration (GFR) depend on :			
A- blood flow	B- PH of the body	C-creatinine level	D-total body fluid

2-Q8: If a drug with a 4 hours half-life is given with an initial dose of 8mcg/ml, assuming first-order kinetics, how much drug will be left at 16 hours?			
A-4 mcg/ml	B-2 mcg/ml	C-1 mcg/ml	D-0.5 mcg/ml

3-Which elimination method involve a constant fraction of drug eliminated per unit time...?			
A-Zero-order elimination	B-first-order elimination	C-Major order elimination	D-All of the above.

4-which one is The amount of blood filtered by the glomeruli in a given time?			
A-harmful competition	**B- Glomerular filtration Rate**	**C-Beneficial competition**	**D-Active Tubular reabsorption**

5-which one can inhibits active tubular secretion of acidic drugs?			
A-probenecid	B-morphine	C-atropine	D-quinine

6-which one of the following is retained in the blood and not filtered?			
A- amino acid	B- glucose	C- water	D-protein

Answers

1	2	3	4	5	6
A	D	B	B	A	D

SAQ

Q1) a patient used atropine for a period of time then he noticed some toxic effects(use for question 1 to 3)
what method should we use to increase the clearance of atropine?

Q2) what is the name of drug used ?

Q3) what is the mechanism of action ?

Q4) what are the Characters of active tubular secretion:

Q5) what are the Factors affecting renal excretion of drugs:

Q6) what are the types of transport and give examples for each one

Answers

A1) Urine acidification method of Ion trapping

A2) Ammonium chloride

A3) it will increase basic drug excretion by urine acidification.

A4) needs energy ,transports drugs against concentration gradients between blood and filtrate, requires carriers,Saturable,Not specific

A5) Slide 7-8

A6) Slide 5

GOOD LUCK!

Team Leaders

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