MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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# Renal Block

Pharmacology Team 438

# Renal Excretion

Editing File

## 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
- 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

**Color Index:**

Red : important

Black :Main content

Pink : in female's slides only

Blue : in male's slides only

Green : Dr's notes

Grey: Extra information , explanation

All the drugs mentioned in this lecture are very important.

# Routes of excretion

**Major routes of excretion**

- Renal excretion
- Biliary excretion

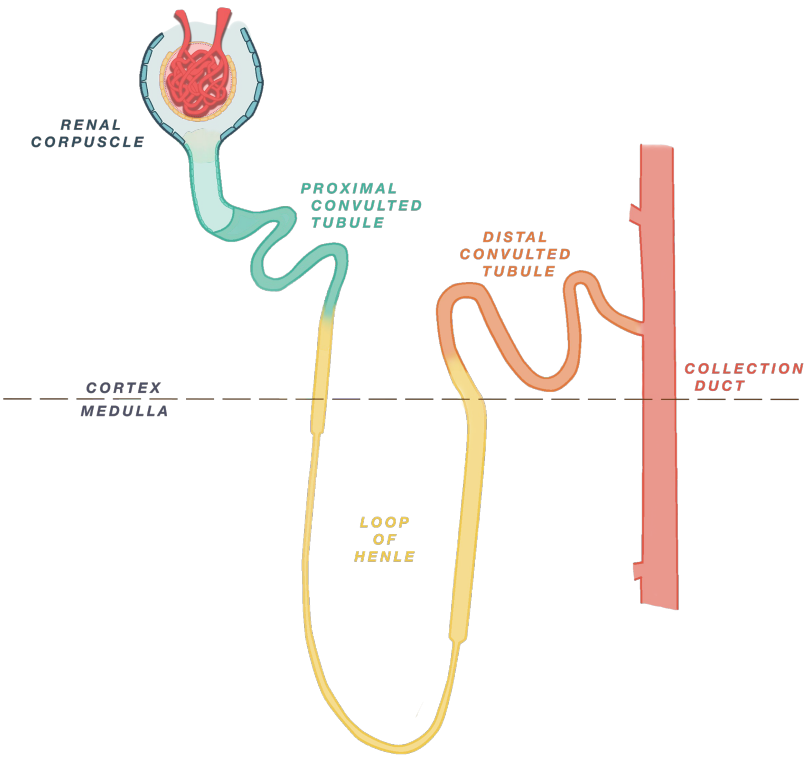
**Minor routes of excretion**

- Pulmonary/ Exhale
- Salivary
- Mammary excretion (Milk)
- Sweat
- Tears

# Structure of the kidney

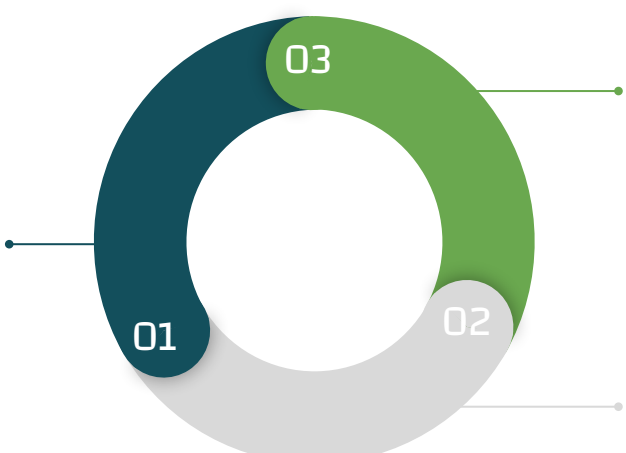
The structural unit of the kidney is the nephron which consists of :

1. Glomerulus
2. Proximal convoluted tubules
3. Loop of Henle
4. Distal convoluted tubules
5. Collecting ducts




Females slides only

# Normal kidney functions




Regulation of electrolytes (aldosterone)

Excretion of wastes & drug metabolites such as: Urea, uric acid, creatinine

Regulation of water balance (antidiuretic hormone)

# Renal excretion

Urinary excretion of drugs occurs through three processes:

1. Glomerular filtration
2. Active tubular secretion
3. Passive or active tubular reabsorption

## 1) Glomerular Filtration

It is the amount of blood filtered by the glomeruli in a given time.

- It depends upon renal blood flow and the hydrostatic pressure in the capillaries.
- Normal GFR = 125-130 ml\min.
- Filtrate **does not** contains blood cells , platelets and plasma proteins.
- Most drugs are filtered through glomerulus
- GFR is determined by creatinine and inulin (inulin is easily filtered by kidney not reabsorbed).

### Glomerular filtration of drugs occurs to:

1. Low molecular weight drugs
2. Ionized or water soluble drugs e.g. aminoglycosides, tubocurarine
3. Free form of the drugs (Unbound to plasma proteins)
4. Drugs with low volume of distribution [1]

## 2) Active Tubular Secretion

- occurs mainly in proximal tubules.
- It increases drug conc. in the Filtrate (lumen), thus drugs undergo active secretion have excretion rate values greater than normal GFR.[2]
- Secretion of ionized drugs into the lumen. E.g penicillin G

### Characters of active tubular secretion

- Needs energy
- Not specific[3] (competition may happens)
- requires carriers (transporters) More details In the next slide
- Saturable
- transports drugs **against** concentration gradients

1)VD: is the ratio of drug amount in tissue to the concentration of drug in blood. ↓ VD means ↓ conc. in tissue and ↑ conc. in blood.
2)for example: if the drug's conc. In the plasma is 6 and its GFR is 4, the active tubular secretion will later add the other 2 molecules to the filtrate, and the drug's excretion rate (6) will be higher than its normal GFR (4).
3) 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

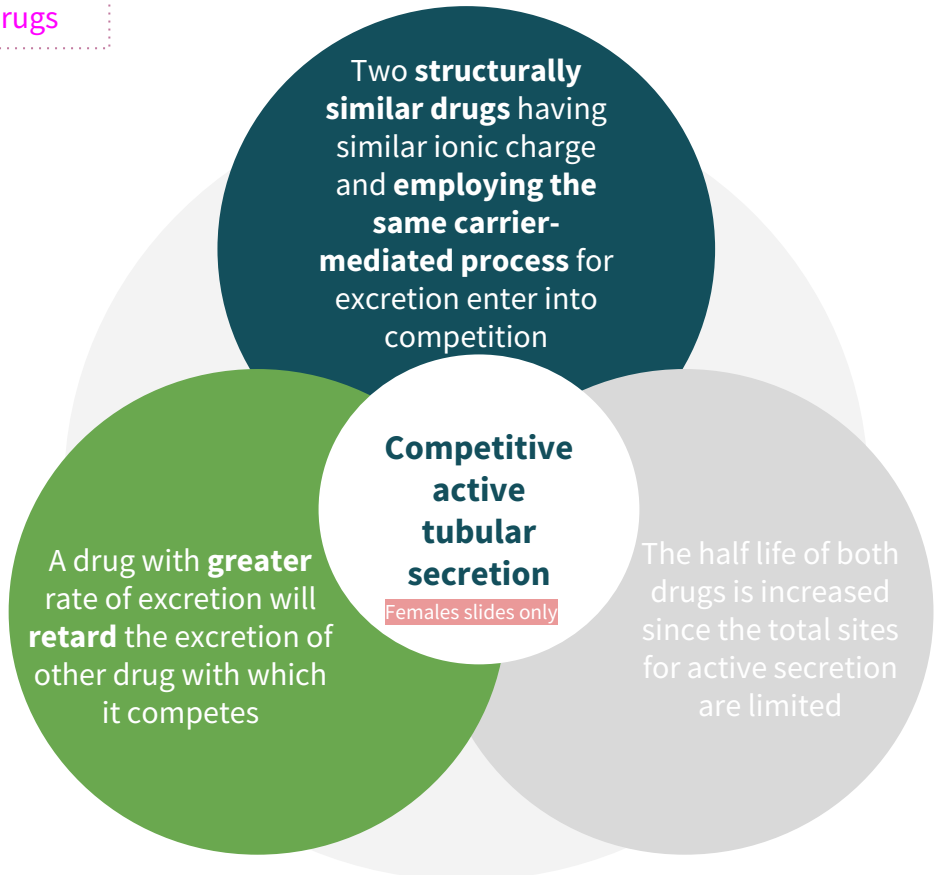
## 1 Transporters for organic acids

Penicillin, aspirin, sulfonamides, uric acid, probenecid

can inhibits active tubular secretion of acidic drugs

## 2 Transporters for organic bases

morphine, catecholamines, atropine, quinine




Two drugs can compete for the same carrier:

- Probenecid & penicillin
- Probenecid & nitrofurantoin

- 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 of penicillin G & increase in its antibacterial action**

**Beneficial competition**

- Probenecid & nitrofurantoin
- Probenecid inhibits renal tubular secretion of nitrofurantoin
  → decreases its efficacy in urinary tract infections (UTIs)[1]

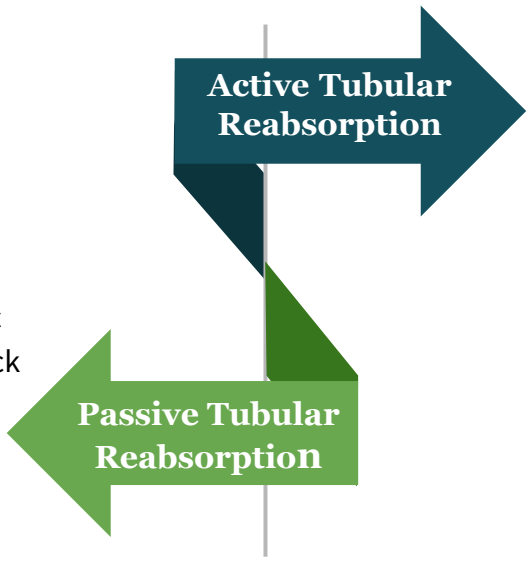
**Harmful competition**

1)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.
- Reabsorption increases half life of a drug
- ★ Reabsorption may be passive **or** active




1. In distal convoluted tubules & collecting ducts.
2. Requires no energy.
3. Passive diffusion of **unionized, lipophilic** drugs reabsorbed back into blood circulation and urinary excretion will be low.
4. Ionized drugs are poorly reabsorbed & so urinary excretion will be High.

1. energy dependant.
2. Occurs with **endogenous** substances or nutrients that the body needs to conserve e.g. glucose, electrolytes, amino acids, vitamins , **uric acid.**
3. Probenecid inhibits active tubular reabsorption of uric acid. So, It increases excretion of uric acid in urine.
4. Probenecid acts as a **uricosuric agent** in the treatment of gout.

# Renal excretion of drugs and pH of urine

1. Normal urine (pH 5.3) is slightly acidic and favors excretion of basic drugs
2. Most of the drugs are weak acids or weak base
3. Changing the pH of urine can inhibit or enhance the passive tubular reabsorption of drugs
4. Most of acidic drugs will be reabsorbed back into the body

# 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, gentamicin)

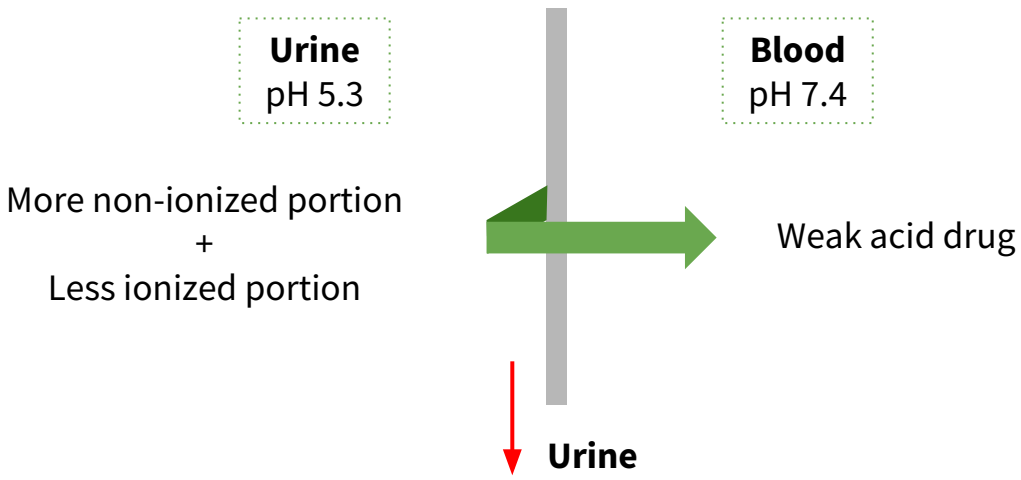
**Urine alkalization**

By sodium bicarbonate (NaHCO3)
increases excretion
of acidic drugs
(aspirin, barbiturates)

## Example of urine alkalization:[1]

**A:**

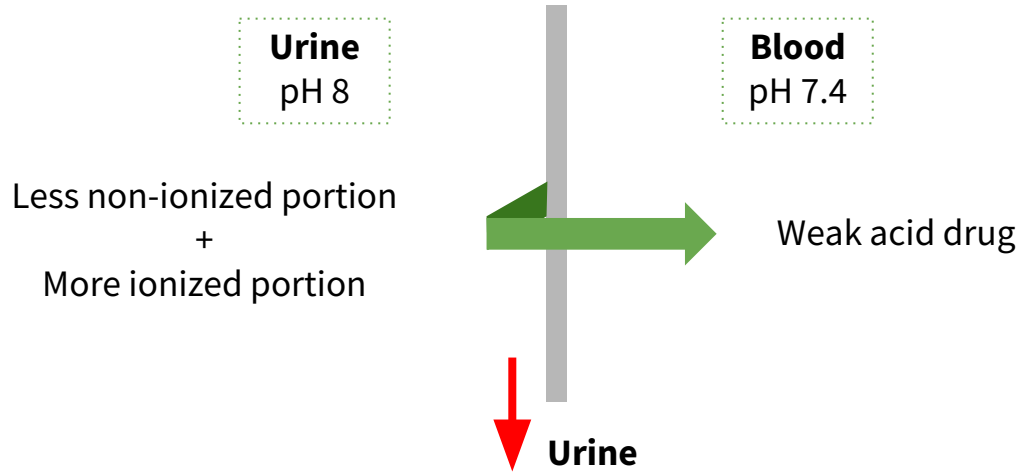
Consider a barbiturate (weak acidic drug) overdose




Most of acidic drug will be reabsorbed back into body

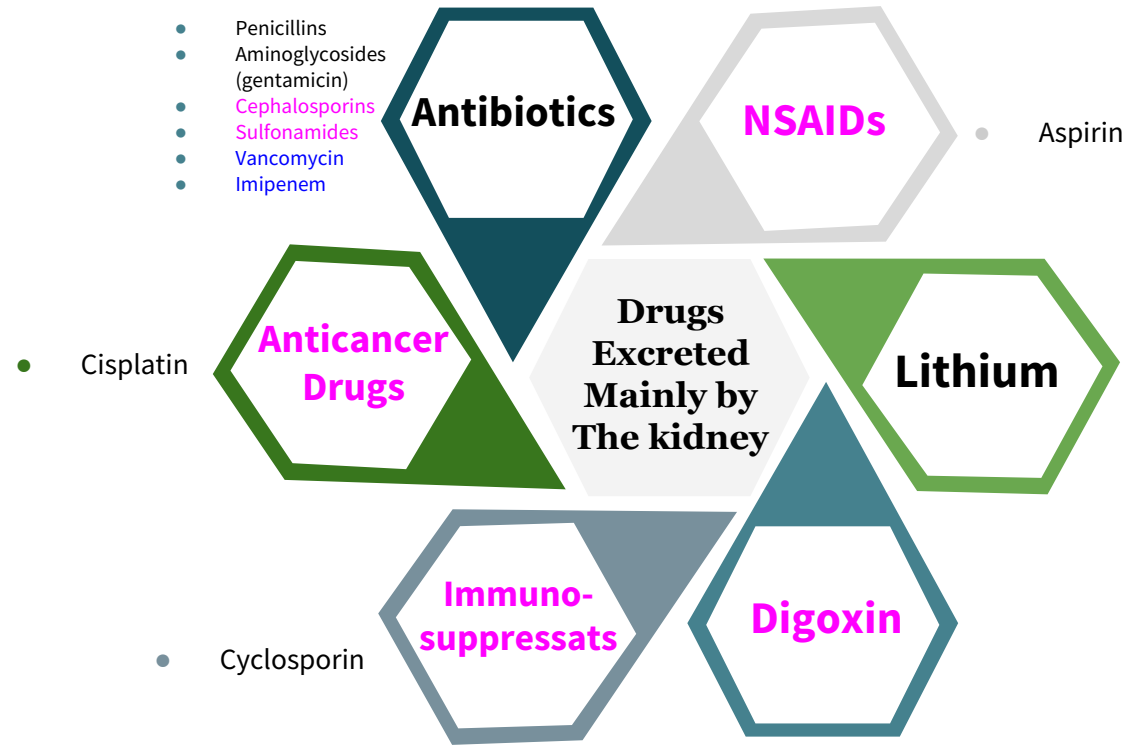
**B:**

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




Most of acidic drug will be eliminated into alkaline urine

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




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

- Renal failure patients
- Elderly patients

| | 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.<br>• Important for drugs:<br>➔ With narrow therapeutic index<br>e.g. lithium, digoxin, warfarin<br>➔ Excreted mainly by the kidney. | • Used to estimate GFR<br>WHY?<br>➔ Because it's produced from muscles and freely filtered. |
| Equation name: | - | **Cockcroft-Gault equation:** |
| Equation | $= \frac{\text{Excretion rate (mg/min)}}{\text{Plasma concentration (mg/ml)}}$ | **For Female :** $= \frac{0.85(140-\text{age})\ BW}{SCr \times 72}$<br>**For Male:** $= \frac{(140-\text{age})\ BW}{SCr \times 72}$ |
| Unit | (ml/min) | |

CrClest = estimated creatinine clearance , BW = body weight , Scr = serum creatinine

# Decreased renal clearance may occur in:

**1 Reduced renal blood flow**

- Congestive heart failure
- Hemorrhage
- Cardiogenic shock

**2 Decreased renal excretion**

- Renal disease (e.g. glomerulonephritis)

**Impaired elimination of drugs may increase half-life (t 1⁄2 ) of drugs**

## So what should we do in this situation ?

1. Dose reduction of drugs is required to prevent toxicity especially with a narrow therapeutic index drugs
2. Keep the usual dose but prolong the dosing intervals. E.g Gentamicin
3. Decrease the dose without changing dosing intervals E.g Digoxin
4. Drugs that are primarily excreted by the kidney need dose adjustment **when creatinine clearance is below 60 ml/min**
5. Minor dose adjustment if CrCl = 30-60 mL/min
   Major dose adjustment if CrCl < 15 mL/min
6. Monitor blood levels of drugs **(therapeutic drug monitoring)**

## 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

➔ Some drugs undergo enterohepatic circulation back into systemic circulation

# Physicochemical factors affecting renal excretion of drug

**Molecular Size**

Larger molecular size of the drugs are more difficult to be excreted than smaller molecular size drugs, especially by glomerular filtration.

**Lipophilicity (lipid solubility)**

Urinary excretion is **inversely** related to lipophilicity ,increased lipid solubility → increase volume of distribution of drug (Vd) and decrease renal excretion.

**Volume of distribution (Vd)**

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

**Degree of ionization of drugs**

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

**Renal blood flow**

Adequate renal function depends upon renal blood flow, thus, renal blood flow is especially important for drugs excreted by glomerular filtration.

- Irrespective of the mechanism of excretion,
Increased perfusion leads to increased contact of drug with secretary site and thus increased excretion.

- Decline in renal blood flow can decrease excretion of drugs.
NSAIDS (e.g. aspirin and ibuprofen) inhibit the production of prostaglandins and therefore reduce renal perfusion and GFR.

**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.

**Biological factors**

**-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.

**Plasma conc.**

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

# Orders of Elimination

**HALF-LIFE**
Is **NOT EQUA**L at two places on the curve

**HALF-LIFE**
Is **EQUAL** at two places on the curve

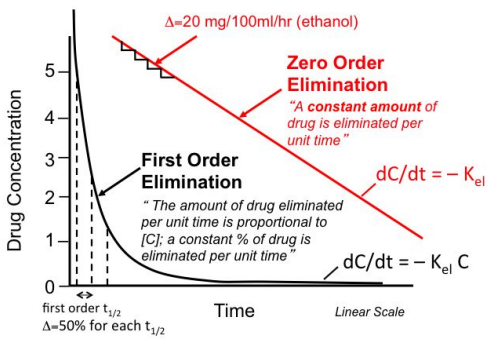
Constant **AMOUNT** is lost per unit time

**Zero-Order**

**First-Order**

Constant **PERCENTAGE** is lost per unit time

**The rate of excretion** is **independent** of the concentration of drugs in the plasma.[1]




**The rate of excretion** is **directly proportional** with concentration of drug in plasma. if the dose is increased, the excretion rate is increased.

**E.g.**
Ethanol(alcohol), phenytoin, aspirin

**E.g.**
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**

**Ans:** 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

01

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

02

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

03

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)

04

Prostaglandins preserve GFR by antagonizing arteriolar vasoconstriction.

1)the rate of elimination remains constant, even if the dosage is increased, this may cause toxicity.

# Quiz

## MCQ

**1-Which one of these drugs follow the first order drug elimination?**

A-Phenytoin B-Aspirin C-penicillin

**2-Which drug reduces renal perfusion and GFR by inhibiting the production of prostaglandins?**

A-ibuprofen B-Probenecid C-Gentamicin

**3-What is the effect of combining Probenecid with nitrofurantoin?**

A-Probenecid activate renal tubular secretion of nitrofurantoin

B-Probenecid inhibit renal tubular secretion of nitrofurantoin

C-Probenecid increase efficacy of nitrofurantoin in UTIs

**4-The renal clearance of a drug is 55 mL/min when the pH of the urine is 8, and 110 mL/min when the pH of the urine is 5. Which of the following is most likely the chemical nature of that drug?**

A-acid B-base C-Non ionizable

**5-Competition between two drugs for active secretion will cause?**

A-Decrease half life of the two drugs B-prolong half life of one of the drugs

C-prolong half life of both drugs D-Decrease half life of one of the drugs

## SAQ

**1-3.LT is a 19-year-old female came to the ER with an infection symptoms after the investigations and blood culture she was diagnosed with streptococcus infection and the doctor decide to start giving her penicillin G.**

**1-Which drug the doctor can give her in combination with penicillin to prolong its half life?**

**2-Before giving her the drug her mother mention that she has a chronic renal failure, will this change the doctor's plan of treatment ? Why ?**

**3-If a drug with a 4-hour half life is given with an initial dose of 20 mcg/ml, assuming First-order kinetics, how much drug will be left at 12 hours?**

**4-SM is a 34-year-old patient used atropine for a period of time then he noticed some toxic effects.What method should we use to increase the clearance of atropine?And what is the name of drug used ?**

**5-Mention one risk factors of NSAIDs that is associated with Acute Renal Failure?**

## Answers

### MCQ's

**Q1-C**

**Q2- A**

**Q3-B**

**Q4-B**

**Q5-C**

### SAQ

**Q1-**Probenecid.

**Q2-**yes, because penicillin is contraindicated or need dose adjustment in renal disease as it excretes mainly by the kidney.

**Q3-** 0.3 mg

**Q4-**Urine acidification method of Ion trapping, Ammonium chloride.

**Q5-**Prostaglandins preserve GFR by antagonizing arteriolar vasoconstriction, A significant reduction in GFR can occur following administration of a NSAID as it inhibits the production of PGs.

pharmacology

Team 438

# Good Luck

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Share with us your ideas !