PHARMACOLOGY
435

PHARMACOLOGY

Lecture 1: Renal Excretion of Drugs

OBJECTIVES:

- Identify main and minor routes of excretion of drugs including renal elimination and biliary excretion
- Describe its consequences on duration of drugs.
- Describe mechanisms involved in renal handling of drugs.
- Describe some pharmacokinetics terms including plasma half life, renal clearance of drugs.
- Describe the correlation between renal clearance and duration of actions of drugs.
- Discuss important factors affecting renal handling (excretion) of drugs
- Know the meaning of urinary ion trapping.
- Be able to identify the influence of age and diseases on renal excretion of drugs.
- Be able to characterize what should be done upon prescribing drugs in patients with renal impairment.

Before studying this lecture we advise you to revise:
pharma: excretion of drugs from the foundation block

- Important.
- Extra notes.
- Mnemonics

Routes of Excretion

Main Routes of Excretion:
- Renal Excretion (kidney is the most important organ for drug excretion)
- Biliary Excretion.

Minor Routes of Excretion:
- Pulmonary (exhalation)
- Salivary excretion
- Dermal (via Sweat)
- Mammary excretion via milk
- Tears

Structure of kidney:

The structural unit of kidney is the nephron, which consists of:
- Glomerulus
- Proximal convoluted tubules (PCT)
- Loop of Henle (Ascending – Descending)
- Distal convoluted tubules (DCT)
- Collecting ducts.

Normal kidney functions:

- Regulation of electrolytes (by aldosterone)
- Regulation of water balance (by anti-diuretic hormone)
- Excretion of wastes & drug metabolites such as: Urea, Uric acid, Creatinine.

Renal Excretion of drugs occur through 3 processes:

1. Glomerular filtration **(most drugs)**
2. Active tubular secretion
3. Passive or active tubular reabsorption

Extra: (from Lippincott)

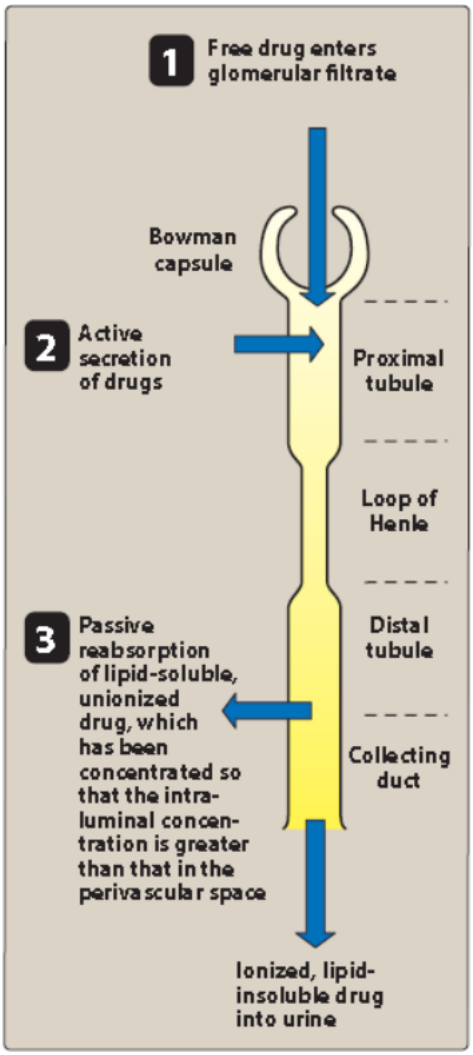


Figure 1.19
Drug elimination by the kidney.

1- Glomerular filtration (GF)

Glomerular filtration (GF) of fluids in general: (physiology)

- Blood is filtered across a semi-permeable membrane into the Bowman's Capsule.
- Driving force for GF is hydrostatic pressure of blood flowing in capillaries.
- 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 (most proteins have high MW (molecular weight) and thus not filtered)

Glomerular filtration rate (GFR) is the amount of blood filtered by the glomeruli in a given time. (Normal GFR = 125-130 ml/min).

- GFR is used as a marker or indicator for kidney function.
- GFR is determined by creatinine, inulin (inulin is easily filtered by kidney & not reabsorbed, This property allows the clearance of inulin to be used clinically as a highly accurate measure of (GFR)).
- Creatinine clearance (CrCl) is used as a marker instead of GFR.

Glomerular filtration of **drugs** occurs to:

- Low Molecular Weight drugs.
- Only free form drugs (unbound to plasma proteins) are filtered.

  The plasma binding drugs have long duration of action. They exist in two forms: (1) the binding form that doesn't have an action and doesn't get filtered nor excreted in the urine , (2) the free form which has an action and gets excreted in urine. when the free form gets excreted the binding form will be converted into free form.

– Polar / ionized / water soluble drugs are easily filtered e.g. penicillin G, aminoglycosides, tubocurarine (muscle relaxant).

  These drugs must be taken by I.V. as they are poorly absorbed orally.

– Drugs with low volume of distribution (Vd)

  these drugs are not distributed in body tissues = higher concentration in plasma = higher concentration will be filtered and excreted.

N.B. Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, variations in GFR and protein binding of drugs do affect this process.

2- Active Tubular Secretion of Drugs

Active tubular secretion

Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule (peritubular capillaries). Active secretion allows rapid elimination of these drugs from the plasma via extraction of the 80% of unfiltered plasma in peritubular capillaries and adding it to the substances that were already in tubule as a result of glomerular filtration.

Characters of active tubular secretion:

- **Active** = Requires energy to transport drugs against concentration gradients between blood and filtrate.
- **Tubular** = Occurs mainly in proximal tubules.
- **Secretion** = Increases drug concentration in tubular lumen (filtrate).
- Secretion of ionized drugs (water soluble) into the lumen e.g. penicillin G.
- It is carrier mediated (by transporters) and saturable,
  secretion is not dose-dependent since there is a limited amount of transporters (saturable), thus, increasing the concentration of the drug in plasma won't increase its secretion and excretion, and thereby it might increase its half life.
- Not specific (competition for the transporter may happen).

Types of transporters (energy-requiring) :	
OAT transporters **For organic acids/anions:**	OCT transporters, **For organic bases/ cations:**
• Penicillin, • Aspirin, • Uric acid, • barbiturates, • sulfonamides, • probenecid (can inhibit active tubular secretion of acidic drugs)	• Morphine (an analgesic and narcotic drug) • Catecholamine (e.g. Isoprenaline) • Atropine (anticholinergic) • Quinine is a medication used to prevent and treat malaria • Gentamicin • Amphetamine note the suffix -ine

2- Active Tubular Secretion of Drugs (cont.)

Two drugs will compete for excretion in the following cases:

a) Drugs using the same carrier (acid/base transporter)
b) structurally similar drugs
c) Drugs with similar ionic charge

A drug with greater rate of excretion will retard (slow/inhibit) the excretion of the other drug which it competes with.
The half life of both drugs is increased since the total sites for active secretion are limited (saturation of the receptor limits further excretion)

❖ **Therapeutic advantages of competition:**

❑ Probenecid & penicillin G

- Both require the same carrier for renal excretion.
- Probenecid competes with (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.
- Why does probenecid win the competition and bind to the receptor instead of other drugs? This is Probably because it has greater affinity for the carrier and greater rate of excretion than most other drugs.

❖ **Therapeutic disadvantages of competition:**

❑ probenecid & nitrofurantoin

- Inhibition of nitrofurantoin secretion by probenecid → decreased efficacy of nitrofurantoin in treatment of UTIs.

Nitrofurantoin is an antibiotic used for treating UTIs. So the drug's site of action is the urinary tract. Thus we need the drug to be more excreted rather than remaining in the plasma. But When Probenecid inhibits its excretion by binding to the carrier transporter, nitrofurantoin will remain more in plasma instead of being excreted, its action is reduced.

Note: Drugs that undergo active secretion have excretion rate values greater than normal GFR. (drug excreted by glomerular filtration + active secretion → more excretion rate). Because at least 80% of the drug delivered to the kidney is presented to the carrier, tubular secretion is potentially the most effective mechanism of renal drug elimination. Unlike glomerular filtration, carrier-mediated transport can achieve maximal drug clearance even when most of the drug is bound to plasma protein.

3- Tubular re-absorption of drugs

Tubular re-absorption of drugs:

- After glomerular filtration, drugs may be reabsorbed back from tubular lumen into systemic blood circulation.
- Tubular reabsorption takes place along all the renal tubules.
- Re-absorption increases half life of a drug.
- Re-absorption may be passive or active:

1. Passive tubular reabsorption:

- In distal convoluted tubules & collecting ducts.
- As a drug moves toward the distal convoluted tubule, water is reabsorbed and thus the drug's concentration increases and exceeds that of the perivascular space. The drug, **if uncharged,** may diffuse out of the nephric lumen, back into the systemic circulation (along concentration gradient "passive"). These drugs will cross membranes, so they must be lipophilic (uncharged).
- Passive diffusion of unionized drugs (lipophilic / lipid soluble) → drug reabsorbed back into blood circulation → **urinary excretion will be low.**
- Ionized drugs (water soluble) are **poorly** reabsorbed → **urinary excretion will be high.**
- water and chloride are passively reabsorbed

2. Active tubular reabsorption :

- Energy dependent (due to active transport)
- Endogenous substances or nutrients that the body needs to conserve (e.g. glucose, electrolytes, amino acids, uric acid, vitamins) are actively reabsorbed.

Probenecid in gout:

It acts as a uricosuric agent* in treatment of gout by suppressing the carrier mediated (active) reabsorption of endogenous metabolite uric acid. Thus, It increases excretion of uric acid in urine.

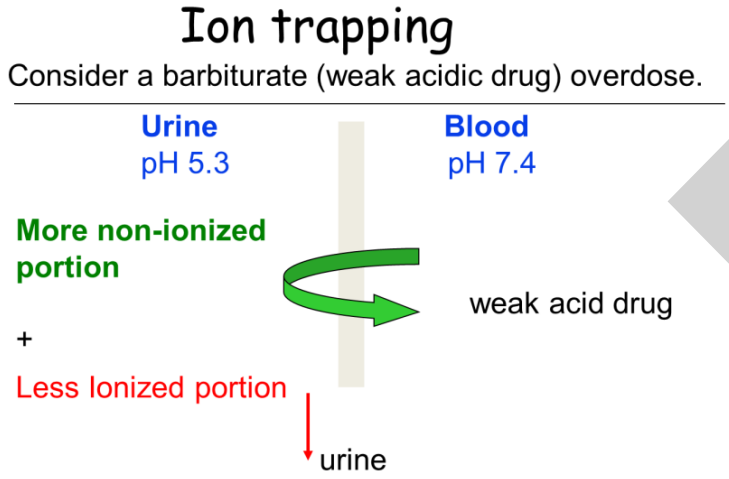
* Uricosuric: a drug which increases uric acid concentration in urine.

Recall (MSk block, NSAIDs): Aspirin in low doses is contraindicated in gout because it blocks secretion of uric acid to urine, leading to increase in plasma uric acid concentration, predisposing to gout.

Renal excretion of drugs and pH of urine (Ion Trapping)

Ion trapping: It is used to enhance renal clearance of a drug during toxicity by Changing pH of urine. This can inhibit or enhance clearance (by changing tubular drug **reabsorption**) of drugs during drug toxicity if stomach lavage is inconvenient. When a drug is in the ionized form, its clearance is enhanced (decreased reabsorption) and vice versa. Manipulating the urine pH to increase the fraction of ionized drug in the lumen may be done to minimize the amount of back diffusion (reabsorption) and increase the clearance of an undesirable drug.

Remember: ● acidic drugs is best ionized (excreted) in basic urine.
● basic drugs is best ionized (excreted) in acidic urine.



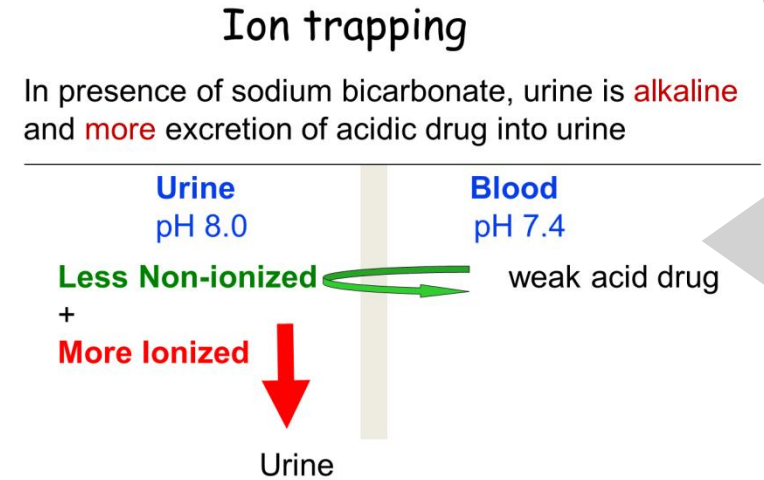
← for example if we consider (a week acid) barbiturate overdose, as we see in the figure, the urine is acidic so an acid drug will not be ionized, instead it will reabsorbed.

مثل أقطاب المغناطيس، المتشابه يتنافر:

Acidic urine + acidic drug = reabsorption into blood

والمختلف يتجاذب:

Acidic urine + basic drug = excretion



← we can have alkaline the urine by giving sodium bicarbonate, we notice an increase in excretion and less reabsorption of acidic drug because the urine is slightly basic now .

Factors affecting renal excretion of drug

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. E.g. Increased lipid solubility → increase volume of distribution of drug (Vd) → decrease concentration of drug in plasma → decrease renal excretion.
	Volume of distribution (Vd):	Renal clearance is inversely related to apparent volume of distribution of drugs. i.e. A drug with large volume of distribution (more concentration in tissues, less concentration in plasma) is poorly excreted in urine. On the other hand, Drugs restricted to blood compartment (low volume of distribution) 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 (no excretion) Dr. Ishfaq slides: The renal clearance of drugs which are extensively bound to plasma proteins is increased **after their displacement** with another drugs. E.g. Gentamicin-induced nephrotoxicity by Furosemide (Furosemide displaces gentamicin from protein → more free drug accumulation in renal tissue) More.
	Plasma concentration:	Glomerular filtration and Reabsorption are directly affected by plasma concentration Of drug.
	Degree of ionization of drugs:	Increased ionization of drug increases its water solubility and thus enhances its renal excretion, Because Polar drugs (water soluble) are easily filtered e.g. aminoglycosides, tubocurarine.

factors affecting renal excretion of drug (cont.)

Renal blood flow	**Adequate renal function depends upon renal blood flow, thus, renal blood flow is especially important for drugs excreted by Glomerular filtration.** • **Increased perfusion** -Irrespective of the mechanism of excretion- 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 (which dilate afferent arterioles) and therefore reduce renal perfusion and GFR, thus decreasing excretion of drugs.
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.
Disease states	Impairs the elimination of drugs, thus may increase half-life (t ½) of drugs. This may occur due to: **-Reduced renal blood flow.** As in Congestive heart failure, Hemorrhage, and Cardiogenic shock. -**Decreased renal excretion,** as in Renal disease (e.g. glomerulonephritis)
Urine pH	-Most drugs are weak acids or weak bases. -Normal urine pH = 5.3 (slightly acidic) and favors excretion of basic drugs. 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. -Most of acidic drugs will be reabsorbed back into body. -Changing the pH of urine can inhibit or enhance the passive tubular re-absorption of drugs: 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).

Renal Excretion & Clearance

❖ **Renal clearance:** Creatinine clearance rate (CrCl) is the unit volume (ml) of plasma cleared by the kidney per unit time (min)..

$$\text{Clearance (CLr) (ml/min)} = \frac{\text{Excretion rate } [C_u V_u]}{\text{Plasma concentration } [Cp]}$$

CLr : renal clearance

C_u : drug concentration in the urine

V_u : volume of urine in 24 hours

Cp : drug concentration in the blood

Creatinine clearance (CrCl) is used to estimate glomerular filtration rate (GFR) because creatinine is produced from muscle (endogenous, unlike inulin) and freely filtered (low MW, water soluble, and is not protein bound).

The Cockcroft-Gault equation for creatinine clearance estimation:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

The second formula is extra, but we'll study in biochemistry any ways. Check the first lecture of biochemistry (kidney function tests) for more details.

Creatinine clearance and drugs excretion

❖ Decrease in renal clearance occurs in:

- CHF
- Hemorrhage
- Cardiogenic shock
- Renal diseases

And this decrease in renal clearance may increase the half life of drugs and may result into drug toxicity .

Renal clearance is especially important for :

- drugs with narrow therapeutic index **(warfarin, lithium ,digoxin)**
- drugs mainly excreted by the kidney. These drugs should be prescribed carefully in **Renal failure patients & Elderly patients**

Drugs excreted mainly by the kidney:
Antibiotics: Penicillins, cephalosporins Aminoglycosides (gentamycin) Sulfonamides, vancomycin imipenem
NSAIDS "aspirin"
CHF "digoxin"
Immunosuppression "cyclosporine"
Anticancer "cisplatin"
psychiatric *medication* "lithium"

❖ In renal impairment what should we do?

1-Choose drug with biliary excretion (excreted mainly into feces) such as doxycycline and ceftriaxone. These drugs **don't need dose adjustment** in renal impairment. Some drugs undergo enterohepatic circulation back into systemic circulation

2-Drugs that are primarily excreted by the kidney **need dose adjustment** when creatinine clearance is below 60 ml/min.

a) Minor dose adjustment if CrCl = 30-60 mL/min.

b) Major dose adjustment if CrCl < 15mL/min.

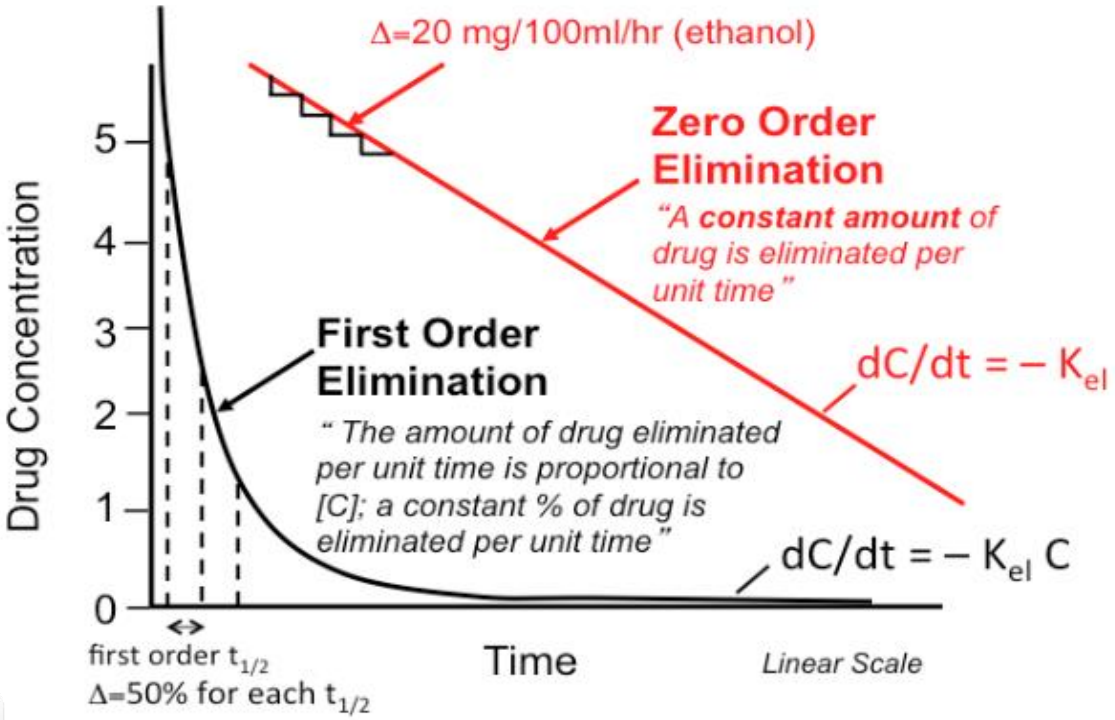
c) Monitor blood levels of drugs (therapeutic drug monitoring).

d) Prolong dose intervals instead of adjusting the dose e.g. (gentamycin)

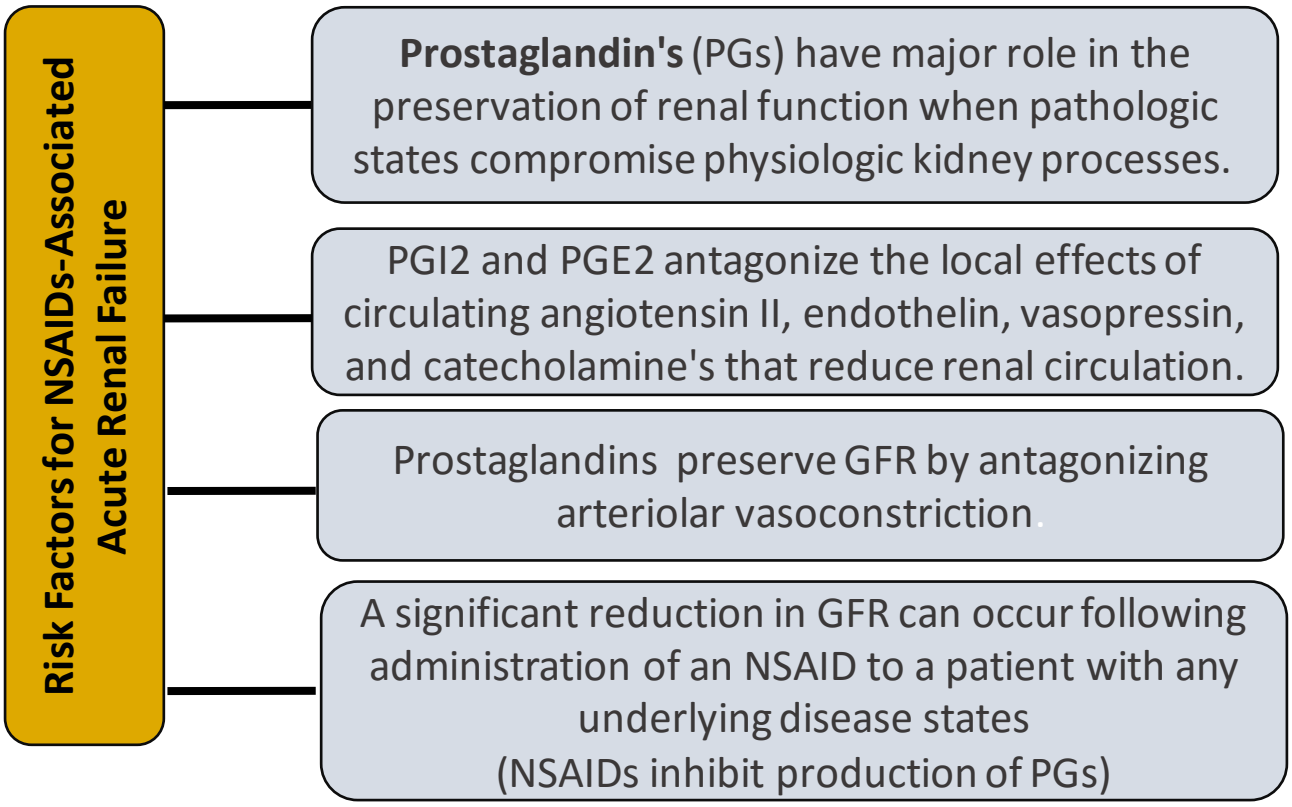
Orders of elimination

Orders of elimination of drugs:

Zero-order	First-order
The half-life is …….. At two places on the curve	
Not equal	**equal**
Constant …….. is lost per unit time	
Amount	**Percentage**
The rate of excretion is…….	
rate of excretion is independent of the concentration of drugs in the plasma. The enzyme is saturated by a high free drug concentration, and the rate of elimination remains constant, even if the dosage is increased, this may increase toxicity of drugs.	**rate of excretion is directly proportional with concentration of drug in plasma.** if the dose is increased, the excretion rate is increased, (that is, with each half-life, the concentration decreases constantly by 50%)
E.g. Ethanol(alcohol), phenytoin, aspirin	**E.g.** penicillin, aminoglycoside , quinolones



Risk Factors for NSAIDs-Associated Acute Renal Failure



Important notes (summary):

- Ion trapping is used to enhance drug clearance
- (aminoglycoside, penicillin, lithium, vancomycin, imipenem) are excreted by the kidney
- Ceftriaxone is excreted by feces
- Renal clearance depends on kidney function
- Decrease in renal clearance because of reduce in renal blood flow
- 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 probenicid.
- Protein binding of drugs inhibits renal excretion of drugs except those that are actively secreted.
- NSAIDS e.g aspirin and ibuprofen inhibit the production of PGs and therefore reduce renal perfusion and GFR.
- Irrespective of the mechanism of excretion renal of drugs , decreased renal blood flow decrease excretion of drugs.

Summary -1

Renal Excretion

Glomerular filtration

Location: glomerulus.

Glomerular filtration (GFR) depend on :

Renal blood flow and the hydrostatic pressure that flow to the capillaries

Glomerular filtration occurs to :

1- Low MW drugs 2 - Only free drugs

3- Polar or ionized or water soluble drugs

4- Drugs with low volume of distribution (Vd)

Active tubular secretion

Location: mainly proximal convoluted tubule

Secretion increases drug conc. In lumen, requires energy, carrier mediated:

1. transporters of Organic acids (e.g. penicillin),
2. transporters of organic bases (e.g. catecholamine)

-Two drugs using the same carrier compete for excretion:

-Advantages of competition:

*inhibition of organic acids secretion e.g. probenecid & penicillin (increasing their conc. In plasma)

-Disadvantages:

*probenecid Decreases nitrofurantoin's efficacy in UTIs.

tubular reabsorption

Passive

- location: distal convoluted tubules & collecting ducts
- Unionized(lipophilic) drugs: highly reabsorbed, poor urinary excretion
- Ionized(hydrophilic)drugs: poorly reabsorbed, high urinary excretion

-basic drugs are ionized in an acidic environment, while acidic drugs are ionized in a basic environment.

- Ion trapping: changing urine pH to enhance reabsorption or clearance of certain drugs (toxicity).

-Urine favors excretion of basic drugs because its slightly acidic.

-Urine acidification:

By NH_4Cl, enhances excretion of basic drugs (e.g., Amphetamine).

-Urine alkalization:

by $NaHCO_3$, increases excretion of acidic drugs (e.g. Aspirin).

Active

- energy dependent

-Endogenous substances or nutrients that the body needs to conserve.(e.g. glucose)

- probenecid acts as a uricosuric in gout (inhibits uric acid reabsorption)

Summary -2

Factors affecting renal excretion of drug:

molecular size	Larger molecular size = less excretion Small molecular size = more excretion
Lipophilicity	Lipid soluble = less excretion. Water soluble = more excretion.
protein binding	Highly protein bound = less excretion. Poorly protein bound = more excretion.
Plasma concentration	High plasma conc. Of drug = more excretion. Low plasma conc. Of drug = less excretion.
Volume of distribution	High volume of distribution = less excretion. Low volume of distribution = more excretion.
Degree of ionization	Polar drugs (water soluble) are easily filtered = more excretion
Renal blood flow	Increase renal perfusion = more excretion. Decrease renal perfusion = less excretion. NSAIDS e.g aspirin and ibuprofen inhibit the production of PGs and therefore reduce renal perfusion and GFR. (may lead to acute kidney injury)
Biological factors	Renal clearance is reduced in neonates and elderly, thus Dose reduction is advisable, otherwise toxicity may occur.
Disease states	Impairs the elimination of drugs, thus may increase half-life (t ½) of drugs. This may occur due to: -Reduced renal blood flow. -Decreased renal excretion.
Urine pH	-Normal urine pH = 5.3 (slightly acidic) and favors excretion of basic drugs. - 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. -Most of acidic drugs will be reabsorbed back into body.

Summary -3

Orders of elimination of drugs:

Zero-order	First-order
The half-life is **Not equal** At two places on the curve	The half-life is **equal** At two places on the curve
Constant **Amount** is lost per unit time	Constant **Percentage** is lost per unit time
rate of excretion is independent of the concentration of drugs in the plasma.	**rate of excretion is directly proportional with concentration of drug in plasma (that is, with each half-life, the concentration decreases by 50%)**
E.g. Ethanol(alcohol), phenytoin, aspirin	**E.g.** penicillin, aminoglycoside , quinolones

Creatinine clearance and drugs excretion

For male :	Female: CrClest
CrClest = (140 − age)BW / SCr × 72	0.85(140 − age)BW / SCr × 72

Renal clearance is especially important for :

- drugs with narrow therapeutic index **(warfarin, lithium ,digoxin)**
- drugs mainly excreted by the kidney. These drugs should be prescribed carefully in **Renal failure patients & Elderly patients**

this decrease in renal clearance may increase the half life of drugs and may result into drug toxicity .

In renal impairment what should we do?

1-Choose drug with biliary excretion: no **dose adjustment** is needed.

2-Drugs that are primarily excreted by the kidney **need dose adjustment:**

Minor dose adjustment if CrClest is 30-60 mL/min

Major dose adjustment if CrClest less that 15 mL/min.

MCQS

Q1- Glomerular filtration (GFR) depend on :

A) blood flow B) PH of the body C)creatinine level D) total body fluid

Q2- Glomerular filtration occurs to :

A) Low MW drugs B) Only free drugs C) Polar or ionized or water soluble drugs D) All correct

Q3:which of these drugs use biliary excretion :

A) Penicillin B) Lithium C) Ceftriaxone D) imipenem

Q4: a patient presenting with phenobarbital (weak acid) overdose can be treated with ……., which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption.

A) *bicarbonate* B) *gentamycin* C) *ammonium chloride* D) *Ceftriaxone*

Q5:A 50-year- old male has a UTI and was given nitrofurantoin for the infection; which of the following drugs would you avoid for administration with nitrofurantoin.

A) Probenecid B) dobutamine C) paracetamol D) Lithium

Q6: which of the following can be used to increase the excretion of gentamicin.

A) Sodium bicarbonate B) ammonium chloride

Q7:Which of the following features will increase the excretion of certain drug?

A) Highly protein-bound. B)Large molecular weight.

C) Small volume of distribution. D) Decrease renal blood flow.

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

Q9: 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

Explanation: Since 50% is lost every 2 h:

2h : 8 mg - 50% = 4 mg

2h : 4 mg - 50% = 2 mg

2h : 2 mg - 50% = 1 mg

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

THANK YOU FOR CHECKING OUR WORK

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For any correction, suggestion or any useful information do not hesitate to contact us :Pharmacology.med435@gmail.com

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