Renal Excretion of Drugs

Prof. Hanan Hagar

Pharmacology unit

Excretion of Drugs

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.**

Routes of Excretion

Routes of Excretion

- **Major routes of excretion**
  - Renal excretion.
  - Biliary excretion.
- **Minor routes of excretion**
  - Pulmonary excretion.
  - Salivary excretion.
  - Mammary excretion via milk.
  - Skin / Dermal excretion via sweat.

Renal Excretion

Structure of kidney

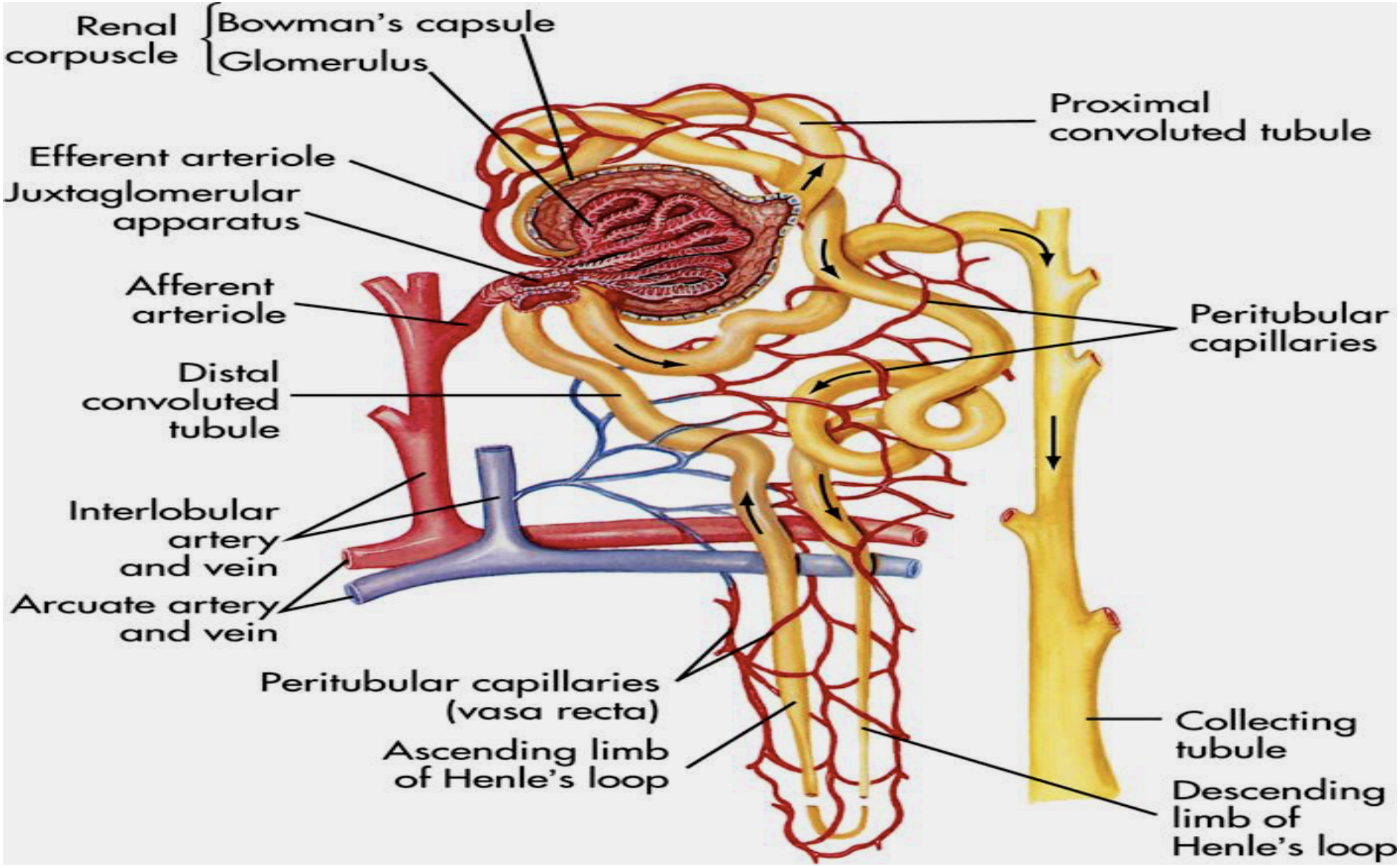
The structural unit of kidney is NEPHRON

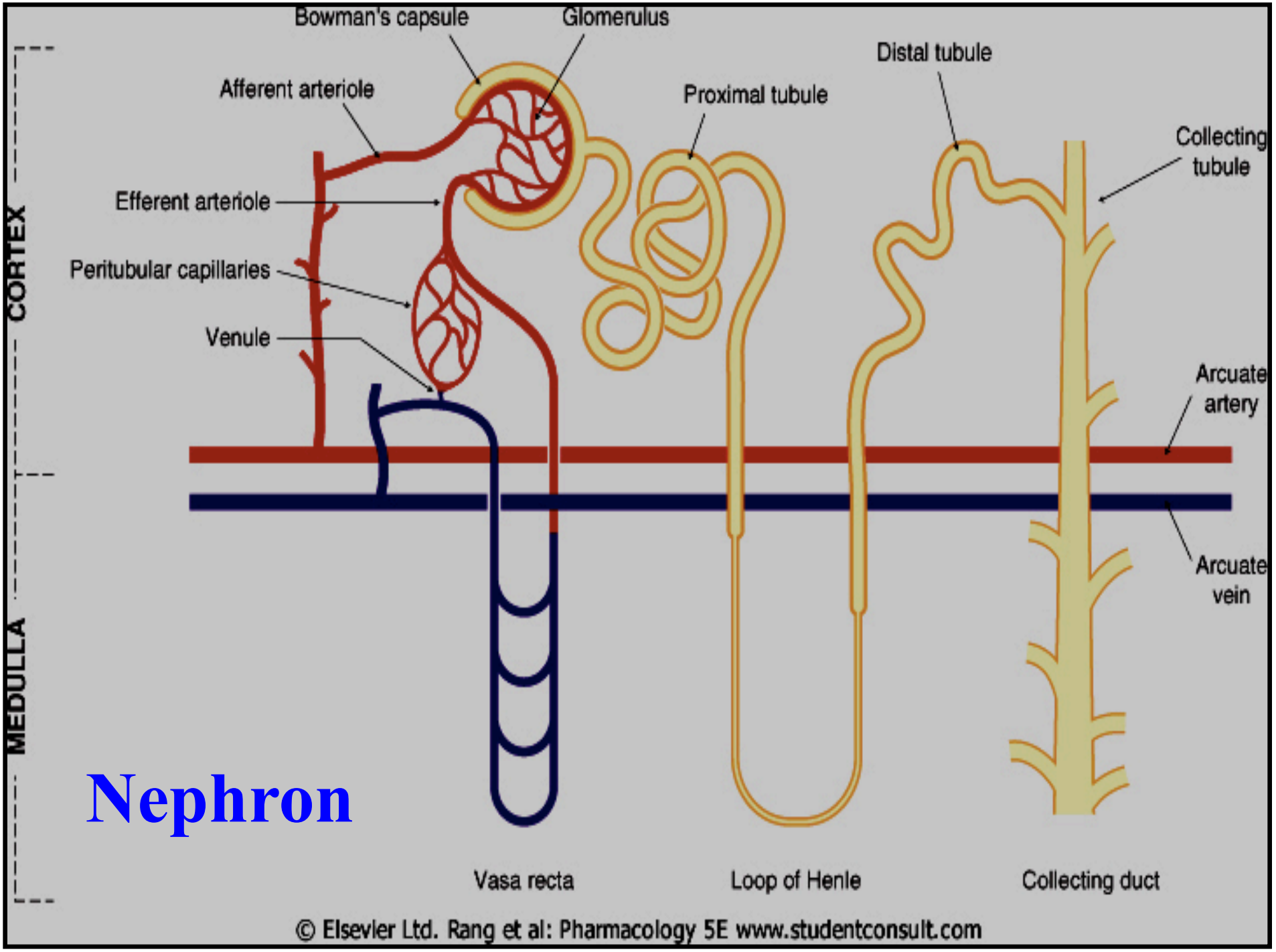
That consists of :

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

Structure of kidney

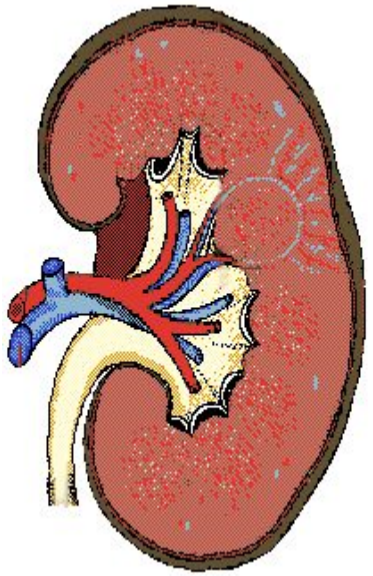
The structural unit of kidney is NEPHRON




Bowman's capsule
Glomerulus
Afferent arteriole
Proximal tubule
Distal tubule
Collecting tubule
Efferent arteriole
Peritubular capillaries
Venule
Arcuate artery
Arcuate vein
CORTEX
MEDULLA
Nephron
Vasa recta
Loop of Henle
Collecting duct
© Elsevier Ltd. Rang et al: Pharmacology 5E www.studentconsult.com

Renal excretion of drugs

- The most important organ for drug excretion is the kidney.



Normal kidney functions

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

Renal excretion of drugs

Urinary excretion of drugs occurs through three processes:

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

Glomerular filtration (GF)

- 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**.

Glomerular Filtration of drugs

- Most drugs are filtered through glomerulus.

Glomerular filtration of drugs occurs to:

- Low molecular weight drugs
- Water soluble drugs e.g. aminoglycosides, tubocurarine
- Free form of the drugs (not bound to plasma proteins).
- Drugs with low volume of distribution (Vd)

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.
- 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 of Drugs

- occurs mainly in proximal tubules
- It increases drug concentration in the filtrate.
- Drugs undergo active secretion have excretion rate values greater than normal GFR.
- Secretion of ionized drugs into the lumen

  e.g. penicillin G

Characters of active tubular secretion:

- needs energy
- transports drugs **against** concentration gradients between blood and filtrate.
- requires carriers (**transporters**)
- Saturable
- Not specific (**competition** may happens).

Types of transporters

- Transporters for organic acids e.g. Penicillin, aspirin, sulfonamides, probenecid.
- Transporters for organic bases e.g. morphine, catecholamines, atropine, quinine.
- **Probenecid** can inhibits active tubular secretion of acidic drugs.
- Two drugs can compete for the same carrier:
  - Probenecid & penicillin
  - Probenecid & nitrofurantoin

Competitive active tubular secretion of drugs

- 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.

Competitive active tubular secretion of drugs

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

Competitive active tubular secretion of drugs

Harmful competition:

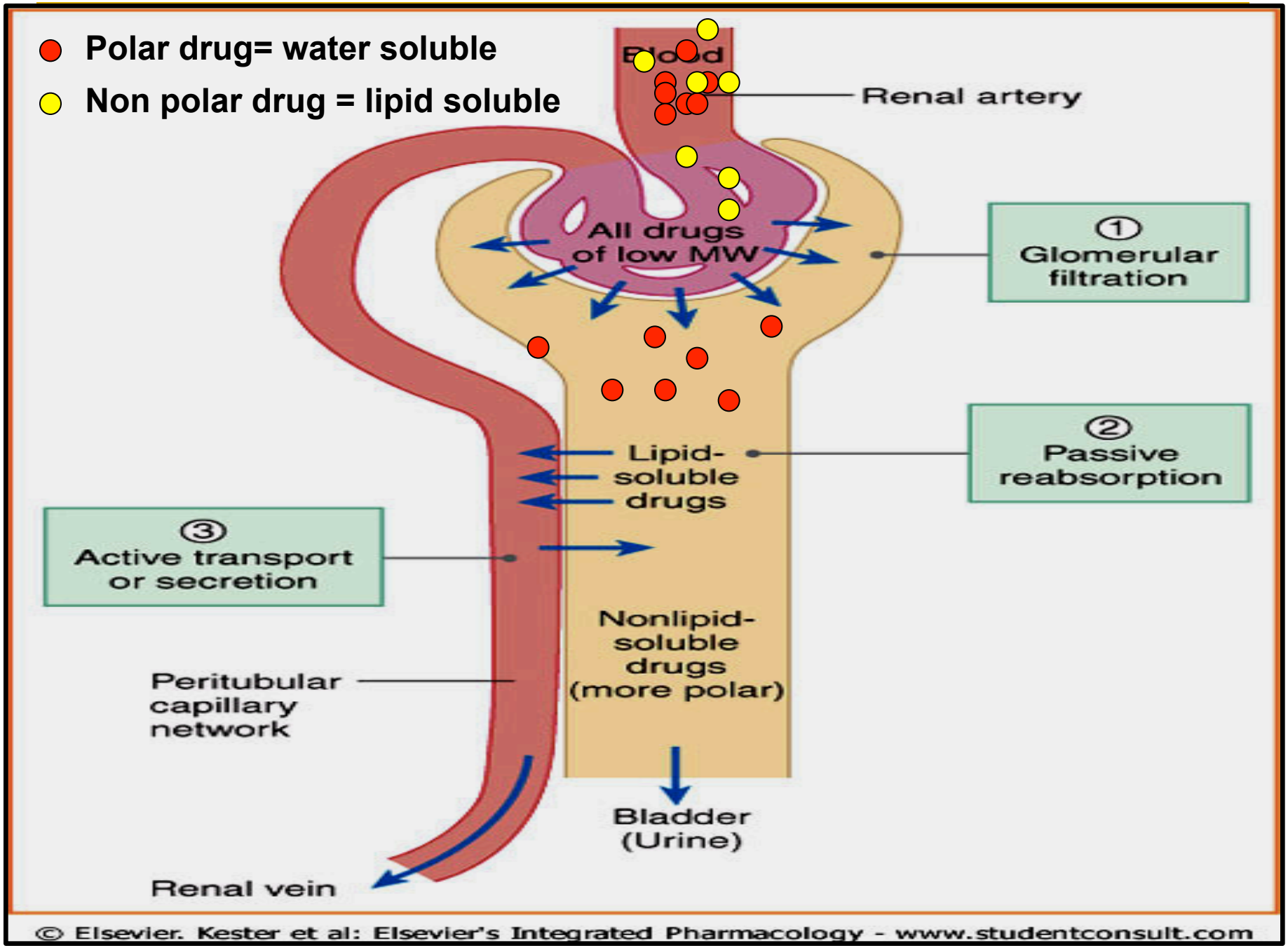
- Probenecid & nitrofurantoin
- **Probenecid** inhibits renal tubular secretion of **nitrofurantoin** thus decreases its efficacy in urinary tract infections (UTIs).

Tubular Re-absorption of Drugs

- After glomerular filtration, drugs may be reabsorbed back from tubular lumen into systemic blood circulation.
- It takes place along all the renal tubules.
- 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 blood (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.


Polar drug= water soluble
Non polar drug = lipid soluble
Blood
Renal artery
All drugs of low MW
① Glomerular filtration
② Passive reabsorption
Lipid-soluble drugs
③ Active transport or secretion
Nonlipid-soluble drugs (more polar)
Peritubular capillary network
Bladder (Urine)
Renal vein
© Elsevier. Kester et al: Elsevier's Integrated Pharmacology - www.studentconsult.com

Active Tubular re-absorption of drugs

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

Factors affecting renal excretion of drugs

- **Blood flow to the kidney**
- **Physiochemical properties of drugs**
  - Molecular weight
  - Lipid solubility
  - Degree of ionization
  - Volume of distribution
  - Binding character
- **Biological factor e.g. age**
- **Disease states**
- **Urine pH**

Factors affecting renal excretion of drugs

1) Renal blood flow:

- 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.

Factors affecting renal excretion of drugs

2) Molecular weight of the drug:

Larger MW drugs are difficult to be excreted than smaller MW especially by glomerular filtration.

3) 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.

Factors affecting renal excretion of drugs

4) 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.

Factors affecting renal excretion of drugs

4) 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.

Factors affecting renal excretion of drugs

5) Binding characteristics of drugs

- 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.

Factors affecting renal excretion of drugs

6) Biological factor:

- 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.

Diseases states

Impairs the elimination of drugs thus may increase half-life (t ½) of drugs. This may occur due to

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

Renal excretion of drugs and pH of urine

- Normal urine pH is 5.3 (Slightly acidic).

- 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.

Renal excretion of drugs and pH of urine

- Most drugs are weak acids or weak bases
- Normal urine (pH 5.3) slightly acidic and favors excretion of basic drugs.
- 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.

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, gentamycin).
- **Urine alkalization:** by sodium bicarbonate NaHCO3 increases excretion of acidic drugs (aspirin).

Ion trapping

Consider a barbiturate (weak acidic drug) overdose.

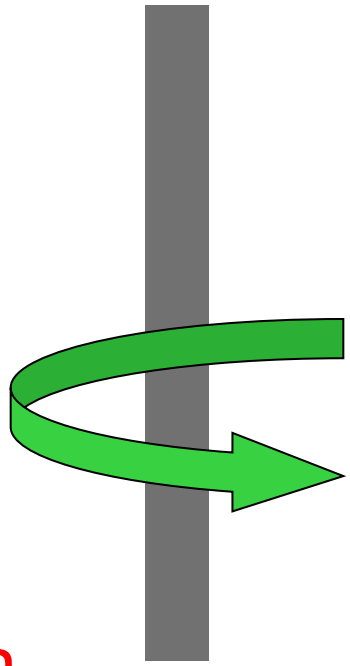
Urine
pH 5.3

Blood
pH 7.4

More non-ionized portion

+

Less Ionized portion



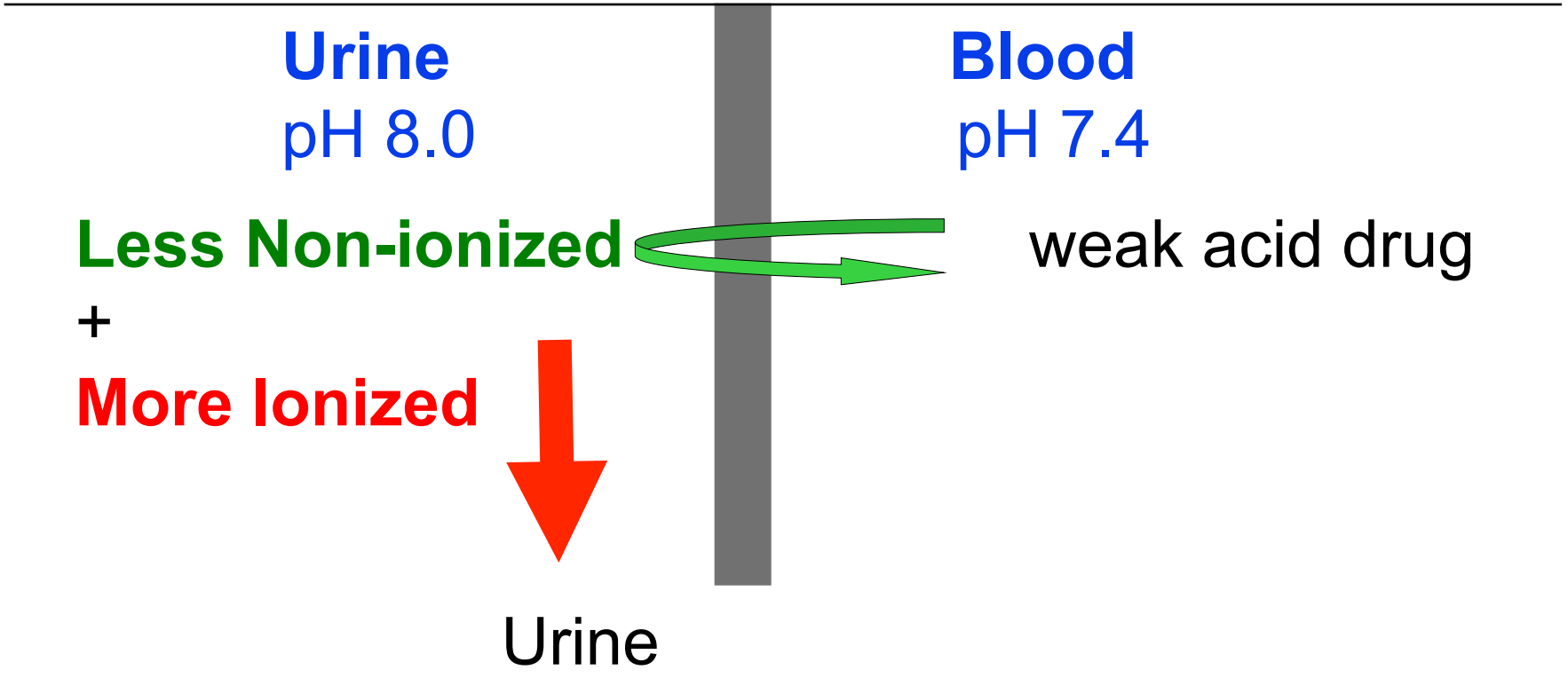
weak acid drug

urine

Most of **acidic drug** will be **reabsorbed back** into body.

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 **alkaline urine.**

Creatinine clearance and drugs excretion

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

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

Renal clearance:

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

CL_r : renal clearance

Cu : drug concentration in the urine

Vu : volume of urine in 24 hours

Cp: drug concentration in the blood

Estimation of Creatinine Clearance

The Cockcroft-Gault equation for estimation of creatinine clearance

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

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

Renal clearance of drugs:

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

- Drug renal clearance is especially important for some drugs which are:

  - Mainly excreted by the kidney

  - Have narrow therapeutic index (**e.g. lithium, digoxin, warfarin**).

Drugs excreted mainly by the kidney include:

Antibiotics:

- Penicillins, cephalosporins
- Aminoglycosides (gentamycin)
- Sulfonamides

NSAIDs e.g. aspirin

Lithium

Digoxin

Immunosuppressants (cyclosporine)

Anticancer drugs (cisplatin)

Be careful upon prescribing those drugs in:

Renal failure patients – Elderly patients

Creatinine clearance and drugs excretion

So what should we do in renal impairment?

- Drugs that are primarily excreted by the kidney need dose adjustment ***when creatinine clearance is below 60 ml/min.***
- Minor dose adjustment if CrCl = 30-60 mL/min.
- Major dose adjustment if CrCl < 15mL/min.
- 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.

Orders of elimination

- For first-order drug elimination, a constant percentage is lost per unit time.
- Most drugs follow the first order kinetic of excretion e.g. pencillin, aminogylcosides , quinolones ect.
- **In first order kinetic:** the rate of excretion increased with increased in concentration of drug in plasma (constant percentage is eliminated per unit time).

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?

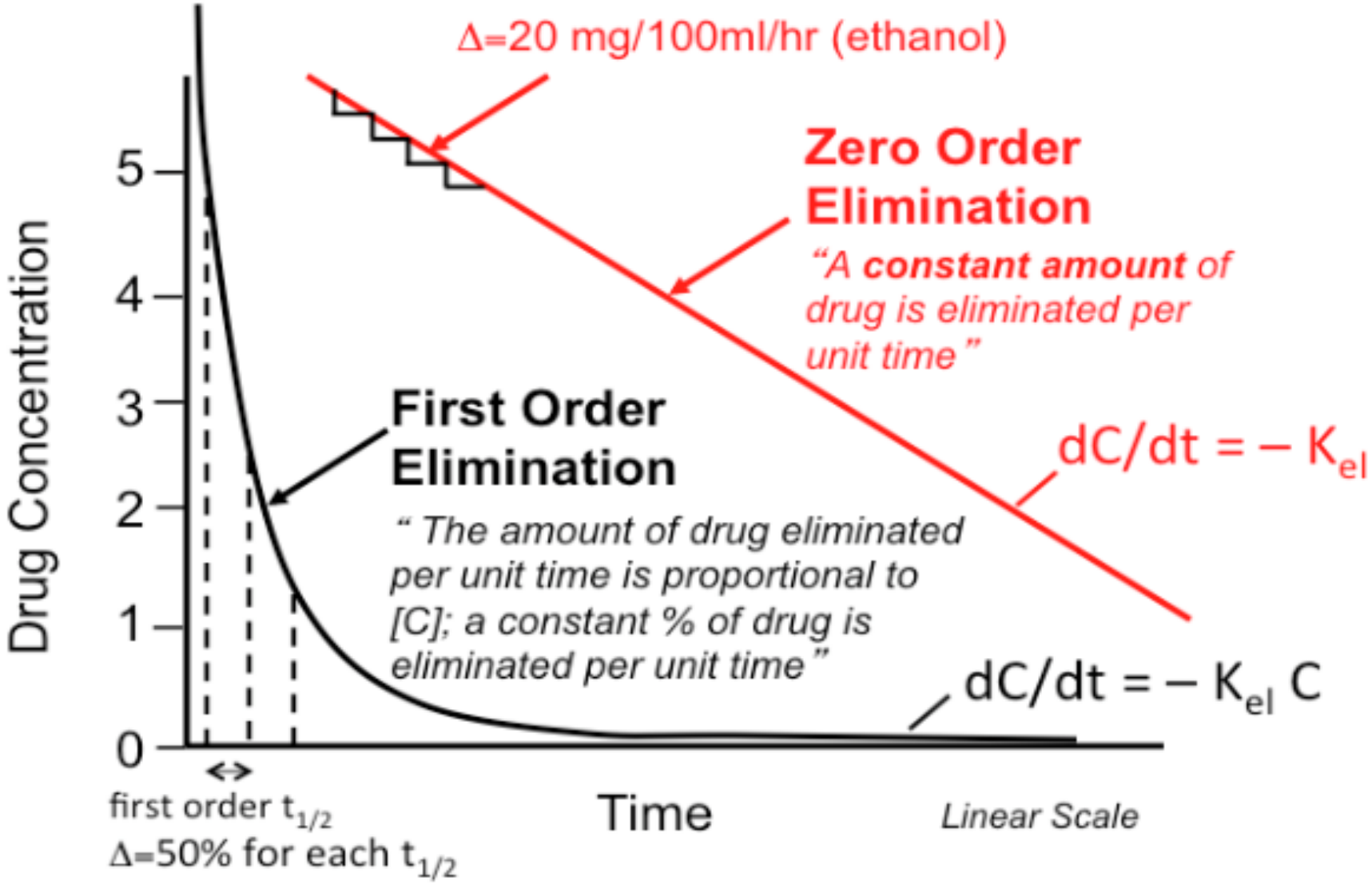
a) 8 mcg/ml
b) 4 mcg/ml
c) 2 mcg/ml
d) 1 mcg/ml

50% is lost every 2 h

2h : 8 mg ⟶ 4 mg
2h : 4 mg ⟶ 2 mg
2h : 2 mg ⟶ 1 mg

Orders of elimination

- For zero-order drug elimination, a constant amount is lost per unit time.
- E.g. Alcohol, phenytoin, aspirin
- In zero order the rate of excretion is **independent** of the concentration of drugs in the plasma (constant amount is eliminated per unit time).


Δ=20 mg/100ml/hr (ethanol)
Zero Order Elimination
"A constant amount of drug is eliminated per unit time"
dC/dt = – K_el
First Order Elimination
" The amount of drug eliminated per unit time is proportional to [C]; a constant % of drug is eliminated per unit time"
dC/dt = – K_el C
Drug Concentration
5
4
3
2
1
0
first order t1/2
Δ=50% for each t1/2
Time
Linear Scale

Risk Factors for NSAIDs-Associated Acute Renal Failure

- Prostagalndins (PGs) have major role in the preservation of renal function when pathologic states compromise physiologic kidney processes.
- PGI_2 and PGE_2 antagonize the local effects of circulating angiotensin II, endothelin,vasopressin, and catecholamines that reduce renal circulation.
- Prostaglandins preserve GFR by antagonizing arteriolar vasoconstriction.
- A significant reduction in GFR can occur following administration of an NSAID to a patient with any underlying disease states (NSAIDs inhibit production of PGs)

Risk Factors for NSAIDs-Associated Acute Renal Failure

- Prostagalndins (PGs) have major role in the preservation of renal function when pathologic states compromise physiologic kidney processes.
- PGI_2 and PGE_2 antagonize the local effects of circulating angiotensin II, endothelin,vasopressin, and catecholamines that reduce renal circulation.
- Prostaglandins preserve GFR by antagonizing arteriolar vasoconstriction.
- A significant reduction in GFR can occur following administration of an NSAID to a patient with any underlying disease states (NSAIDs inhibit production of PGs)

Summary

- 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.

Summary

- Protein binding of drugs inhibits renal excretion of drugs except those that are actively secreted.
- NSAIDS e.g aspirin and ibuprofen inhbits the production of PGs and thefore reduces renal perfusion and GFR.
- Irrespective of the mechanism of excretion renal of drugs , decreased renal blood flow decrease excretion of drugs.

Questions?

E-mail: hananhhagar@yahoo.com