Renal Excretion of Drugs

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Routes of Excretion

Main Routes of Excretion

- Renal Excretion
- Biliary Excretion

Minor Routes of Excretion.

- Exhaled air (Exhalation)
- Salivary
- Sweat
- Milk
- Tears

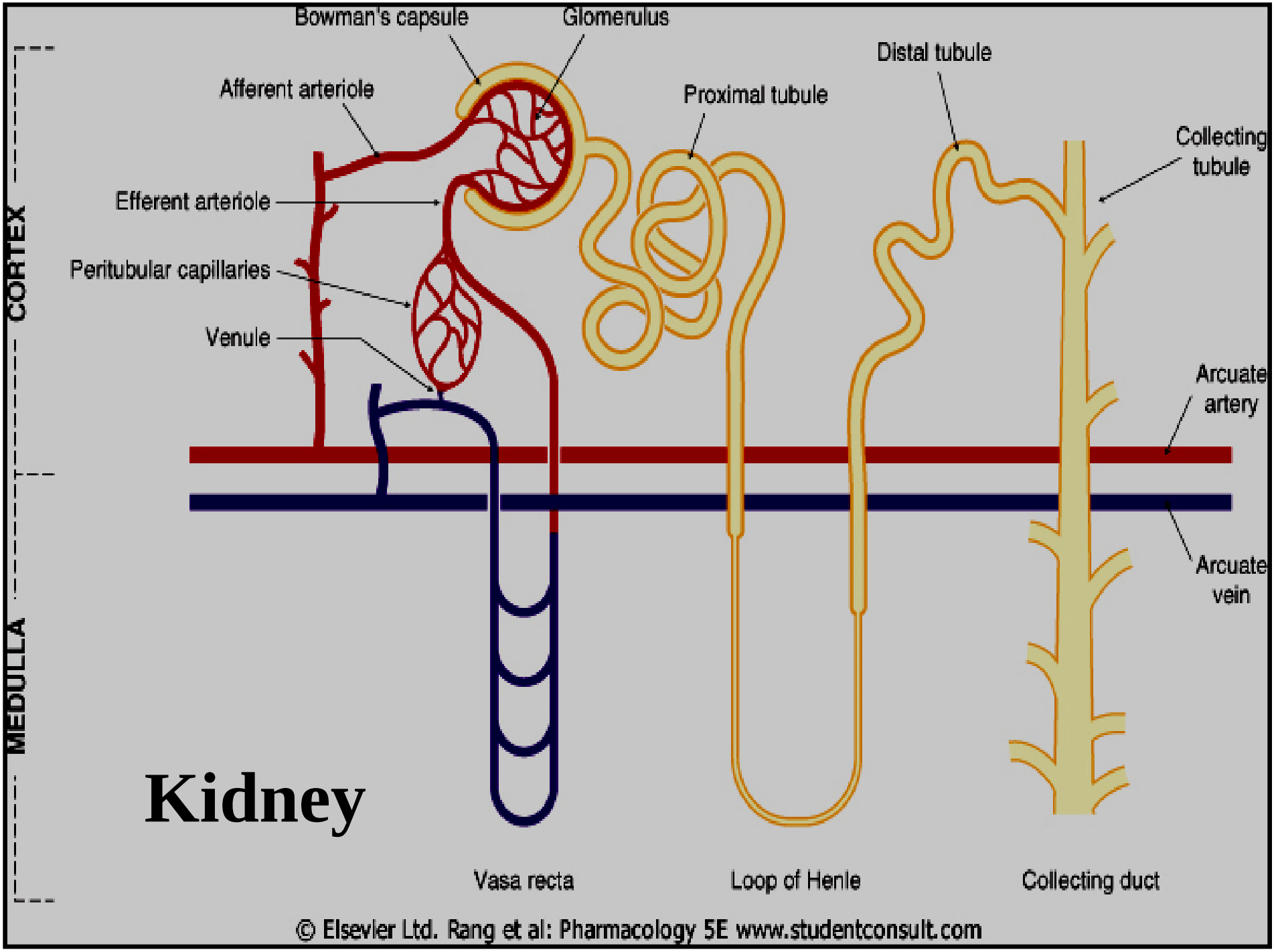
Renal Excretion

Structure of kidney

The structure unit of kidney is nephron

That consists of :

- **Glomerulus**
- **Proximal convoluted tubules**
- **Loop of Henle**
- **Distal convoluted tubules**
- **Collecting ducts**


Bowman's capsule
Glomerulus
Afferent arteriole
Proximal tubule
Distal tubule
Collecting tubule
Efferent arteriole
Peritubular capillaries
Venule
Arcuate artery
Arcuate vein
CORTEX
MEDULLA
Kidney
Vasa recta
Loop of Henle
Collecting duct
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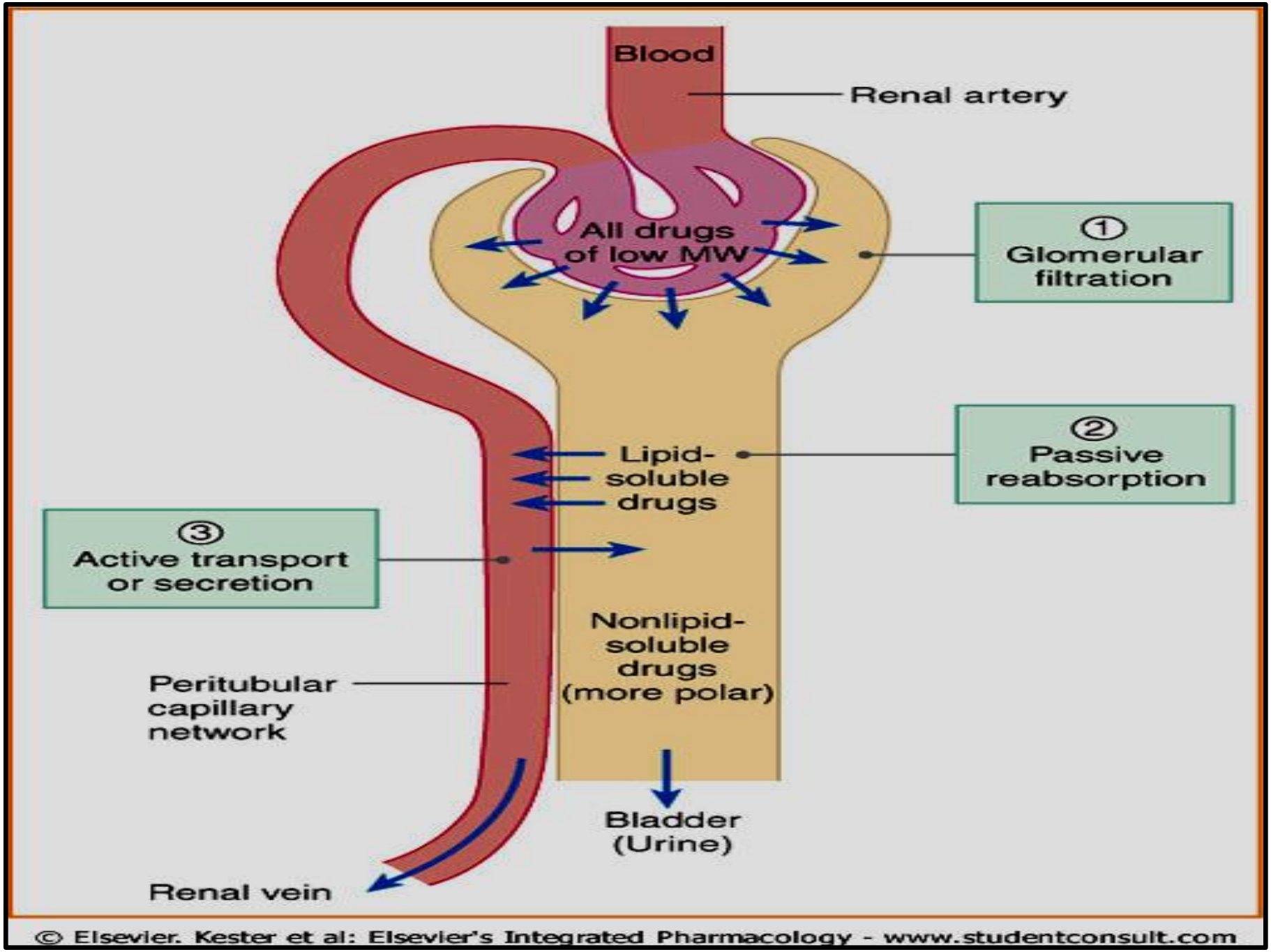
Renal Excretion includes

- **Glomerular filtration**
- **Active tubular secretion**
- **Passive or active tubular reabsorption**



Glomerular filtration (GFR):

- **Depends upon renal blood flow (Normal GFR = 125-130 ml/min).**
- **GFR depends on hydrostatic pressure of blood flowing in the capillaries.**
- **Glomerular filtration occurs to**
  - **Low MW drugs (most proteins have high MW and are not filtered)**
  - **Only free drugs (unbound to plasma proteins) are filtered.**
  - **Polar or ionized or water soluble drugs are easily filtered e.g aminoglycosides**
  - **GFR is determined by creatinine, inulin, inulin is easily filtered by kidney not reabsorbed .**

ActiveTubular secretion:

- **occurs mainly in proximal tubules; increases drug conc. in lumen**
- **It is carrier mediated and saturable**
- **Requires energy to transport drugs against conc. gradients.**

ActiveTubular secretion:

- **Organic acids/anions e.g Penicillin and aspirin, uric acid**
- **Organic bases/cations e.g morphine, catecholamine are actively secreted**
- **Two drugs using the same carrier compete for excretion e.g probenicid increases half life of penicillin .**

Active tubular secretion

- Therapeutic advantages of competition: Probenicid inhibits active tubular secretion of organic acids e.g. Penicillin, increases their plasma conc. 2 fold.
- Probenecid acts as a uricosuric agent in treatment of gout.
- It suppresses the carrier mediated reabsorption of endogenous metabolite uric acid.
- Therapeutic disadvantages of competition: Inhibition of nitrofurantoin secretion by probenecid decreased efficacy in UTIs

Passive tubular reabsorption

- **In distal convoluted tubules & collecting ducts.**
- **Passive diffusion of unionized, lipophilic drugs reabsorbed back into blood circulation and urinary excretion will be Low.**

- **Ionized drugs are poorly reabsorbed & so urinary excretion will be High.**

Active Tubular Reabsorption

- Active Tubular Reabsorption (energy dependant):
- Endogenous substances or nutrients that the body needs to conserve. e.g. glucose, electrolytes, amino acids, uric acid

Tubular re-absorption and Urinary pH trapping (Ion trapping)

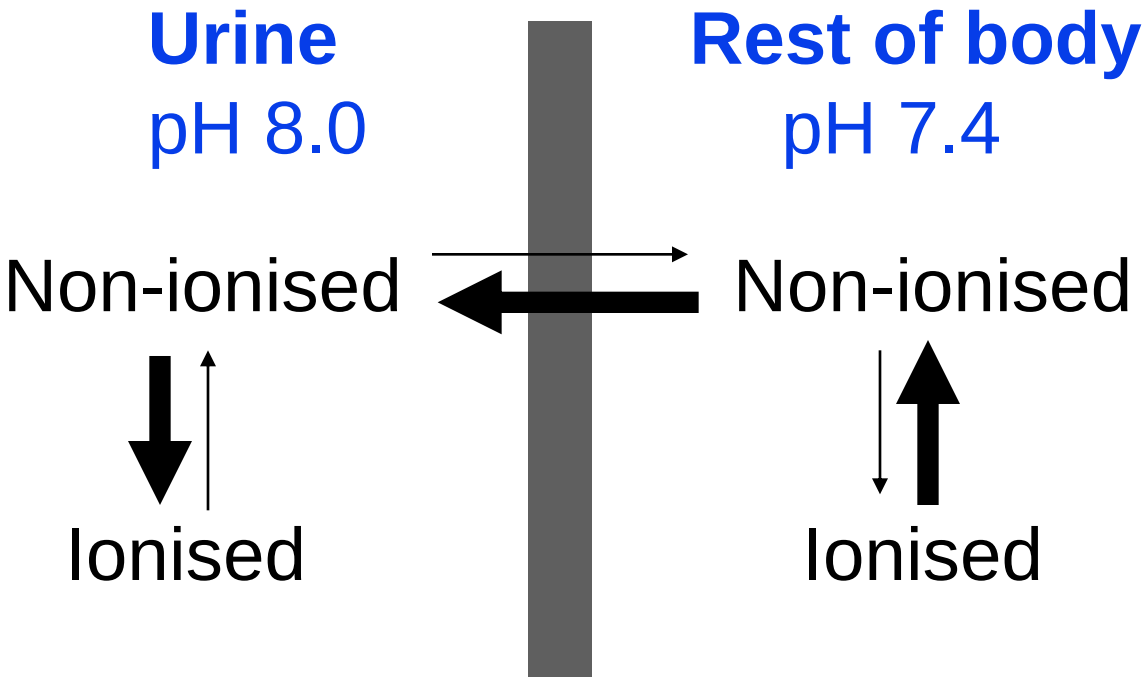
Most of the drugs are weak acids or weak base, changing pH of urine can inhibit or enhance the tubular drug reabsorption.

- **used to enhance renal clearance of drugs during toxicity.**
- **Urine is normally 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.**

- **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).**

Ion trapping

Urine pH varies (4.5 - 8.0). Consider a barbiturate (weak acidic drug) overdose. Sodium bicarbonate may be given to make the urine alkaline



Barbiturate moves into urine - eliminated from body.

Renal Excretion

Drugs excreted mainly by the kidney include:

- **Aminoglycosides antibiotics (Gentamycin)**
- **Penicillin**
- **Lithium**
- **Vancomycin**
- **Imipinem**

These drugs may be contraindicated or need dose adjustment

- **Renal disease.**
- **Elderly people**

Biliary Excretion

- **Occurs to few drugs that are excreted into feces. e.g ceftriaxone is mainly excreted via bile and doest need dose adjustment in renal impairment.**
- **Some drugs undergo enterohepatic circulation back into systemic circulation**

Drug renal clearance:

- Renal clearnce is the unit volume (ml) of plasma cleared by the kidney per unit time (min).

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

- Renal clearance of many drugs and their metabolites depends on adequate renal function.
- Renal clearance is especially important for some drugs with narrow therapeutic index (e.g. lithium, digoxin, warfarin).

Decreased renal clearance may occur in:

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

This may increase half-life (t ½) of drugs

So what should we do in this situation?

- Dose reduction of drugs is required to prevent toxicity especially with a narrow therapeutic index drugs.
  - Dose adjustment is needed when the creatinine clearance is below 60 mL/min.
  - keep the usual dose but prolong the dosing intervals (e.g. gentamicin)
  - decrease the dose without changing dosing intervals (e.g. digoxin)

So what should we do in this situation?

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

Physicochemical factors affecting renal excretion of drug.

- molecular size
- lipophilicity
- ionization
- protein binding
- Plasma concentration
- Volume of distribution
- Renal blood flow

Factors Affecting Renal Excretion

- a) Drug Molecular size: larger molecular size of the drugs are difficult to be excreted than smaller molecular size especially by glumerular filtration.
- Drug lipid solubility: urinary excretion is inversely related to lipophilicity, increased lipid solubility increase volume of distribution of drug and decrease renal excretion.
- Plasma Conc. Glomerular filtration and Reabsorption are directly affected by plasma concentration Of drug
- **Distribution and binding characteristics of the drug**: Clearance is inversely related to apparent volume of distribution of drugs. A drug with large V d is poorly excreted in urine. Drugs restricted to blood compartment have higher excretion rates

Factors Affecting Renal Excretion

- Renal blood flow (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 increased excretion.
- Protein-Drug binding: The renal clearance of drugs extensively bound to plasma proteins is increased after displacement with another drugs. E.g. Gentamicin induced nephrotoxicity by Furosemide .. (Furosemide displaces gentamicin from protein)

- Alteration of urine pH: Discussed before

Orders of elimination

- For first-order drug elimination, half-life t(1/2) is equal at two places on the curve and

  a constant percentage is lost per unit time.

- Most drugs follow the first order kinetic of excretion e.g pencillin, amino gylcoside , quinilones ect.

- In first order kinetic the rate of excretion increased with increased in concentration of drug in plasma.

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, half-life t(1/2) is not equal at two places on the curve and a constant amount is lost per unit time.
- E.g. Ethanol, phenytoin, aspirin

- In zero order the rate of excretion is independent of the concentration of drugs in the plasma.

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)

Creatinine clearance and drugs excretion

The Cockcroft-Gault equation for creatinine clerance estimation

Male: $$CrClest = \frac{(140 - age)BW}{SCr \times 72}$$

Female: $$CrClest = \frac{0.85(140 - age)BW}{SCr \times 72}$$

CrClest= estimated creatinine clearnce, BW= body wieght, Scr= serum creatinine

Minor dose adjustment if CrClest is 30-60 mL/min, Major dose adjustment if CrClest less that 15 mL/min.

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*).**
- **Enterohepatic circulation prolongs half life of the drug.**
- **Inulin and creatinine are used to assess renal function.**

Summary

- **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 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?