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

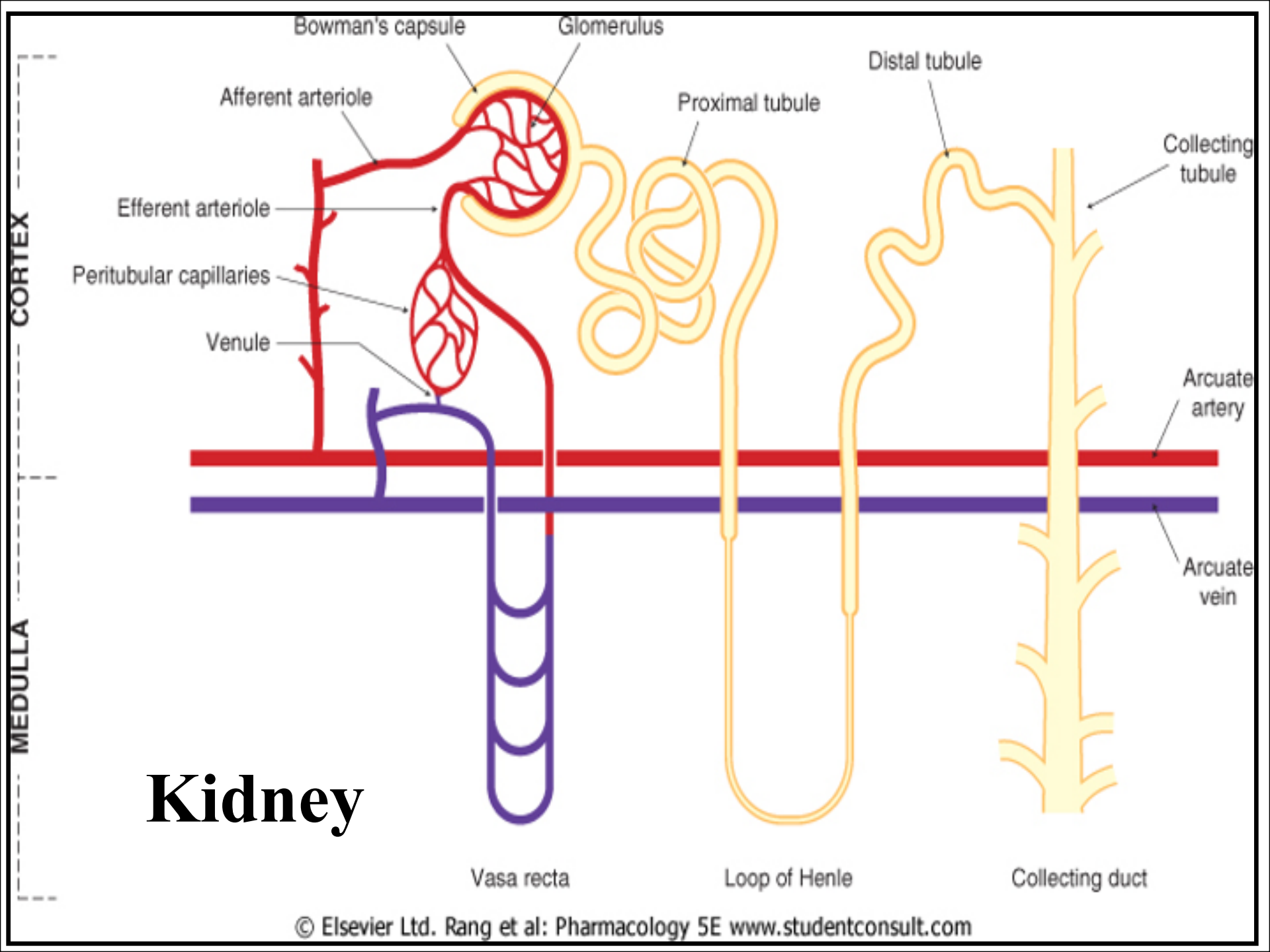
Renal Excretion

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
Vasa recta
Loop of Henle
Collecting duct
Kidney
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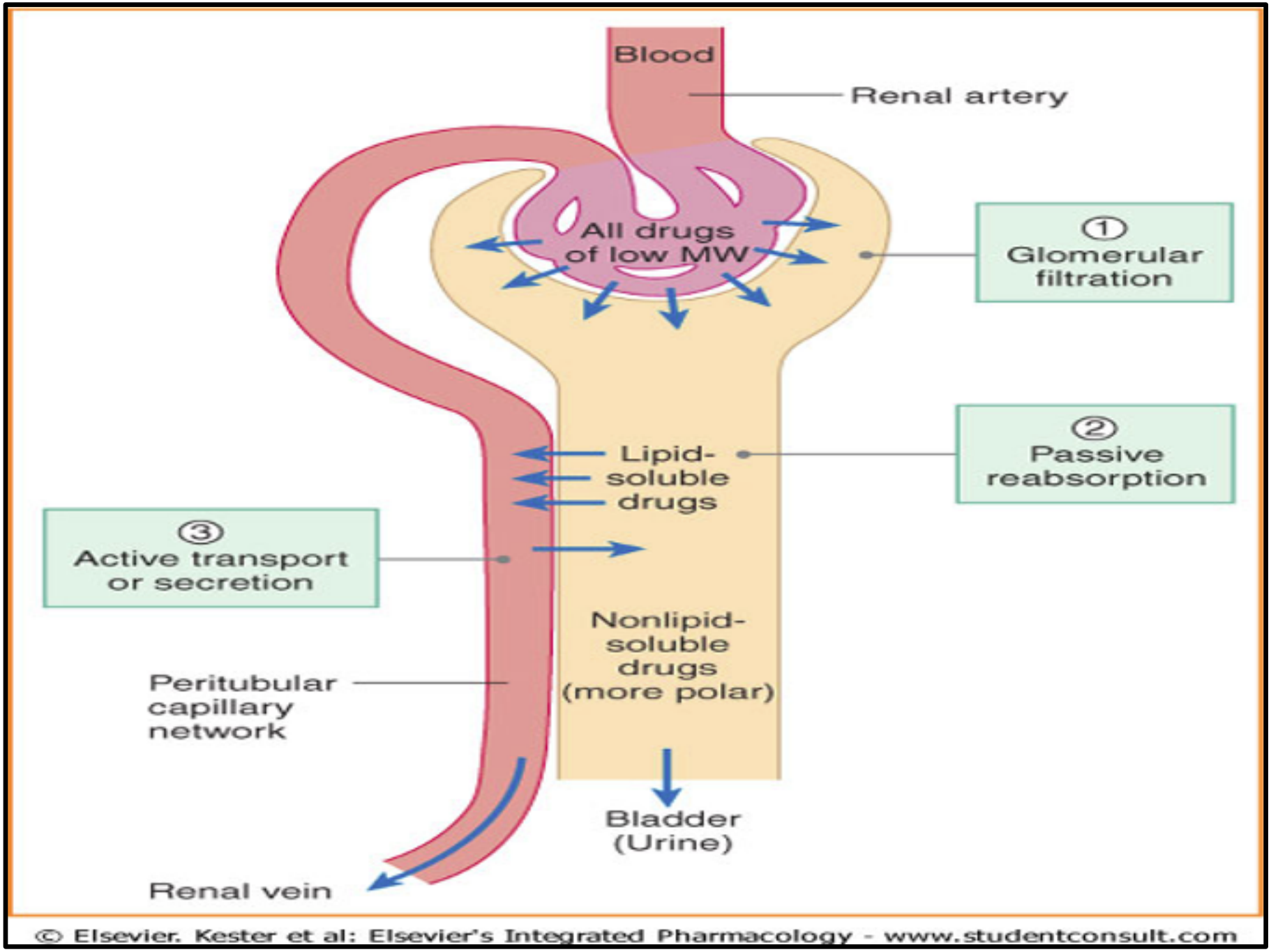
Renal Excretion includes

- 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)

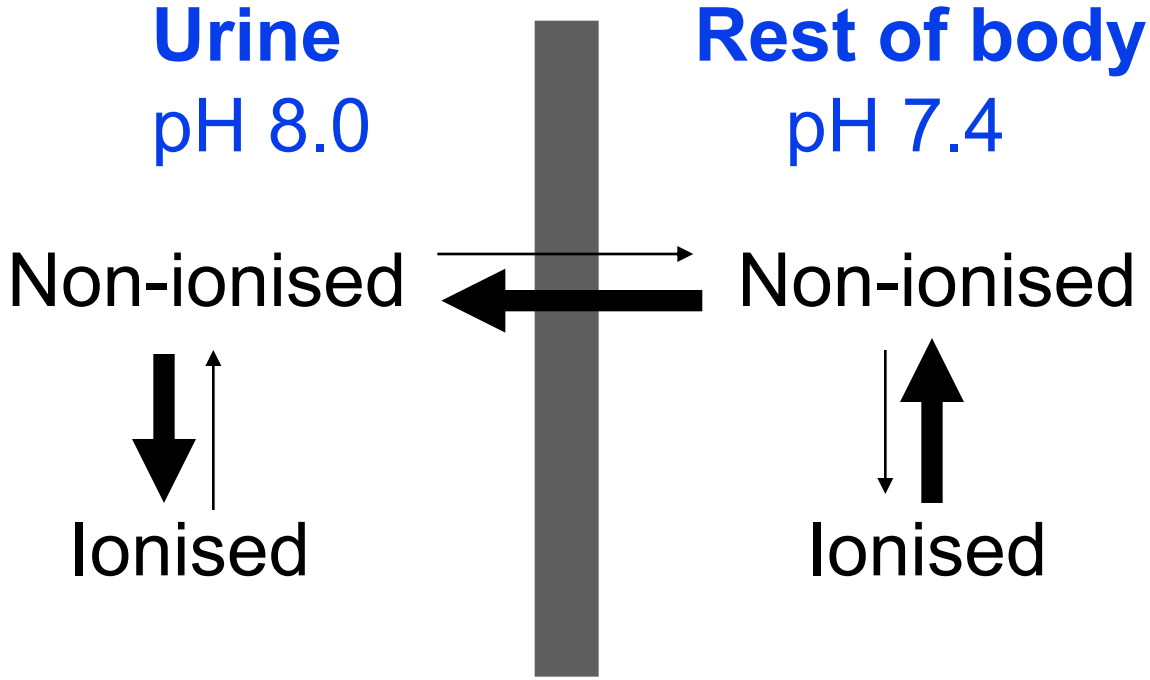
Most of the drugs are weak acids or weak base, changing pH of urine can inhibit or enhance the tubular drug reabsorption.

- **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-**For self Reading**

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?