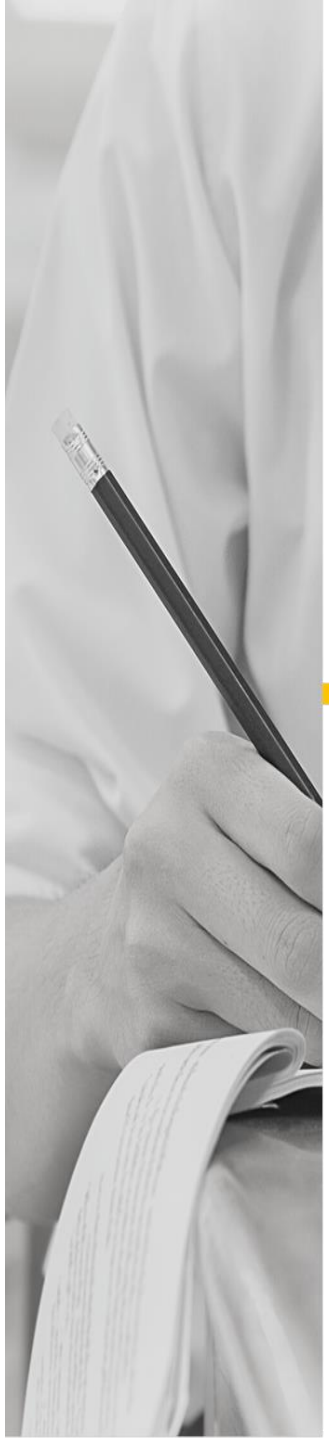

Tikrit University
College of Veterinary Medicine

Subject name:DRUG EVALUATION

Subject year: MSc - PHARMA

Lecturer name: MICRO. ASSAY

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Subject name:Advanced Pharma

Subject year: MSc - PHARMA

LECTURER : Prof Dr Husamuldeen Alnajar

Lecture name: DIURETICS.

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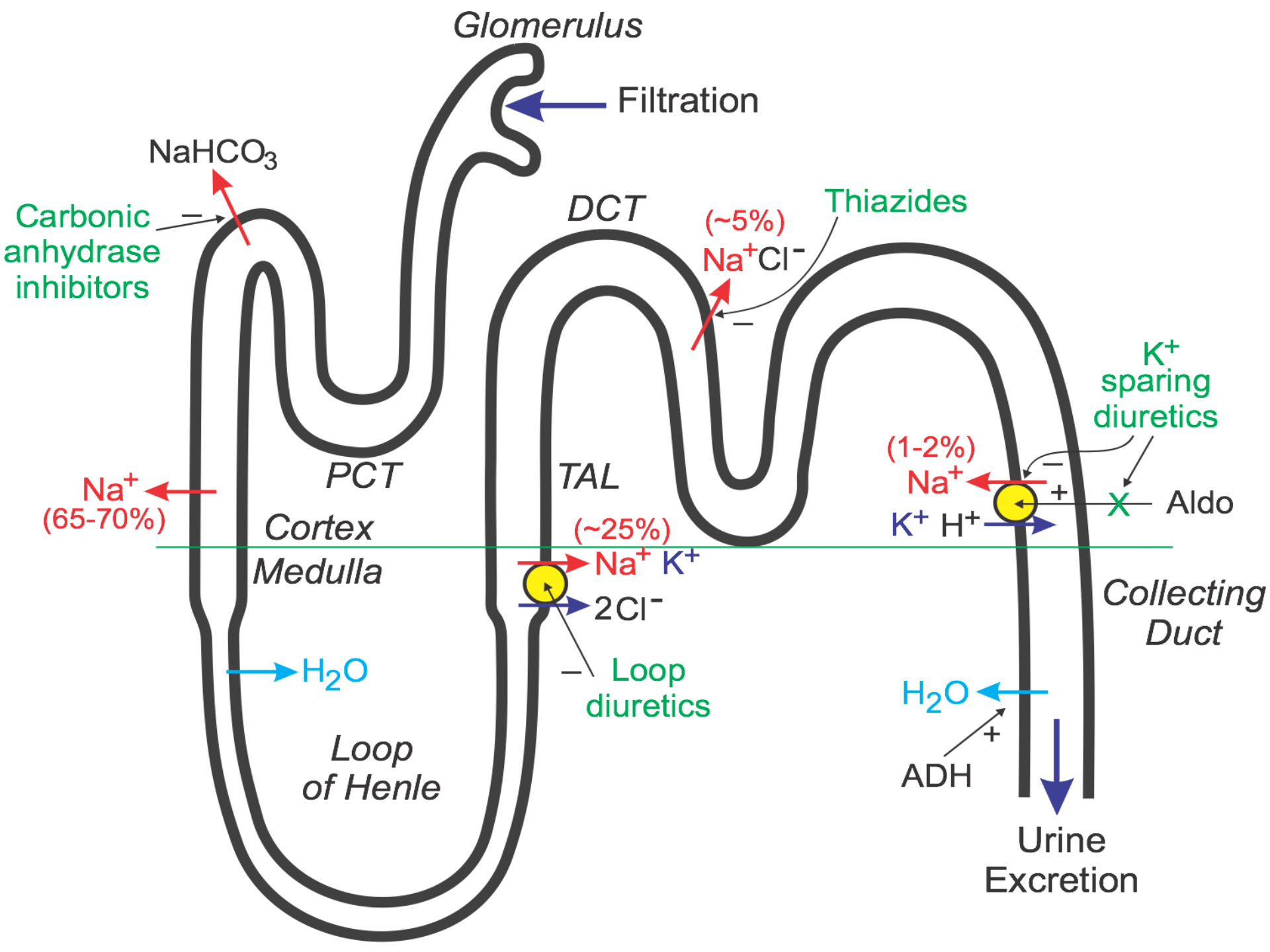
TIKRIT UNIVERSITY
COLLEGE OF VET. MEDICINE

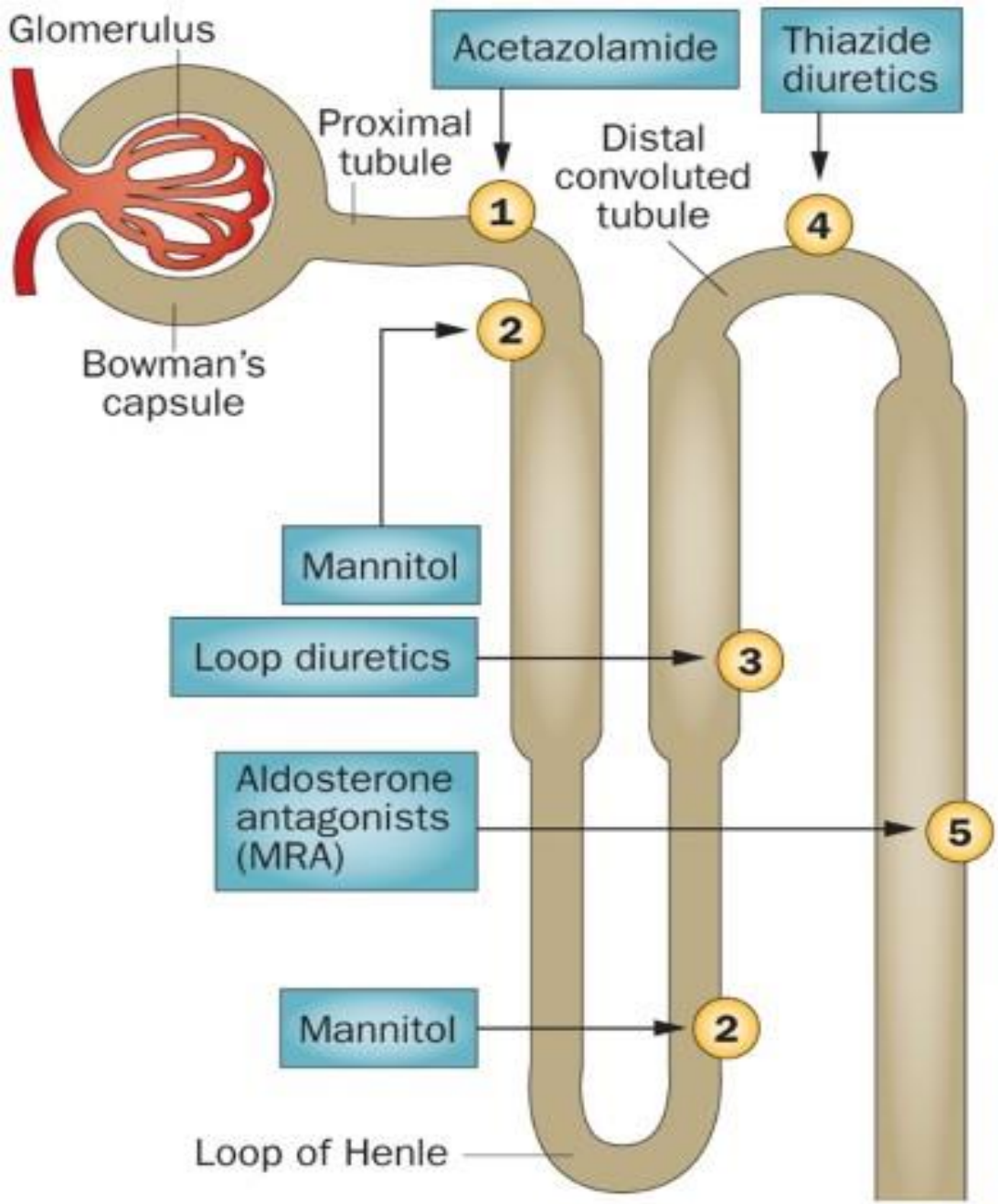
FIRST TERM – M.Sc PHARMACOLOGY
ADVANCED PHARMACOLOGY

PROF DR HUSAMULDEEN ALNAJAR

DIURETICS DRUGS

- **Diuretics are the drugs which increase the rate of urine formation by acting directly on the kidney causing a net loss of solute (mainly NaCl) along with equivalent volume of water, by interfering with transport mechanism responsible for the reabsorption of solutes from various parts of the nephron.**


Glomerulus
Filtration
NaHCO3
Carbonic anhydrase inhibitors
DCT
(~5%) Na+Cl−
Thiazides
K+ sparing diuretics
(1-2%) Na+
K+ H+
X
Aldo
Na+ (65-70%)
PCT
TAL
Cortex
Medulla
(~25%) Na+ K+
2Cl−
Loop diuretics
Collecting Duct
H2O
Loop of Henle
H2O
ADH
Urine Excretion



1 **Blocks carbonic anhydrase**
↑ $NaHCO_3$ excretion

2 **Osmotic diuretic**
↑ H_2O excretion

3 **Blocks sodium-potassium-chloride cotransporter**
↑ Na excretion
↑ K excretion
↑ Cl excretion

4 **Blocks sodium-chloride transporter**
↑ NaCl excretion

5 **Antagonises aldosterone receptor**
↑ Na excretion
↑ K retention

- **NORMAL REGULATION OF FLUIDS & ELECTROLYTES BY THE KIDNEYS**

- **Renal transport mechanisms**

in Proximal tubule NaHCO3 , NaCl, glucose, amino acids and other organic solutes are reabsorbed (specific transport systems).

Water is reabsorbed passively.

luminal fluid osmolality remain constant.

Organic acid secretory system in middle third of proximal tubule. uric acid, NSAIDs.

- **Loop of Henle : Thin descending limb of Henle's loop Water is extracted hypertonic medullary interstitium. Thin ascending limb is water impermeable but is permeable to solutes Na+ /K+ , 2Cl- co transport Driving force for re absorption of Mg+ and Ca2+**
- **Distal Convoluted tubule**
  Na+ and Cl- co transport , Calcium reabsorption under parathyroid hormone control.
- **Collecting tubule system**
  2-5% of NaCl reabsorption, Mineralocorticoids exert significant influence, Important site of K+ secretion .

DIURETICS CLASSIFICATION (ACCORDING TO MECHANISM OF ACTION)

1\ DRUGS INTERFERING WITH IONIC TRANSPORT:

Carbonic Anhydrase inhibitors

Acetazolamide, Dichlorphenamide, Methazolamide

2\ INHIBITORS OF ACTIVE TRANSPORT OF CHLORIDE:

THIAZIDES: Hydrochlorothiazide

Thiazide –related compounds : Chlorthalidone

3\ LOOP DIURETICS: are diuretics that act on the Na-K-Cl cotransporter along the thick ascending limb of the loop of Henle in nephrons of the kidneys. They are primarily used in medicine to treat hypertension and edema often due to congestive heart failure or chronic kidney disease.

Carboxylic acid derivative:

Furosemide (Lasix)

Bumetanide

Torsemide

Phenoxyacetic acid derivative: Ethacrynic acid

4\ POTASSIUM SPARING DIURETICS: drugs that cause diuresis without causing potassium loss in the urine. They are typically used as an adjunct in management of hypertension, cirrhosis, and congestive heart failure. The steroidal aldosterone antagonists can also be used for treatment of primary hyperaldosteronism.

Aldosterone antagonist:(Aldosterone receptor blockers)
Spironolactone

Non-aldosterone antagonist: Amiloride, Triamterene

5\ OSMOTIC DIURETICS: is a type of diuretic that inhibits reabsorption of water and sodium. They are pharmacologically inert substances that are given intravenously. They increase the osmolarity of blood and renal filtrate. This fluid eventually becomes urine.

Mannitol, Urea, Glycerine, Isosorbide

6\ DRUGS INCREASING GFR (SECONDARY DIURETIC):

Xanthines (Aminophylline Theophylline Caffeine)

CLASSIFICATION OF DIURETICS ACCORDING TO SITE OF ACTION

- **Drugs Acting on Proximal Tubule:**

Osmotic Diuretics Carbonic Anhydrase Inhibitors

Acidifying Salt , Xanthine Diuretics

- **Drugs Acting on Ascending Limb of Loop of Henle:**

Loop Diuretics Drugs Acting on Distal Tubule:

Thiazide Diuretics

- **Drugs Acting on Collecting Tubule: K+ - Sparing Diuretics:**

Aldosterone Antagonists

Non – Aldosterone Antagonists

ADH Antagonists.

CARBONIC ANHYDRASE INHIBITORS

CHEMISTRY sulfonamide derivatives SO2NH2 (sulfonamide group) is essential for activity.

PHARMACOKINETICS

- **Oral absorption is good**
  Half life is 6-9 hrs , Route of elimination is mainly renal

- **MECHANISM OF ACTION**: SODIUM BICARBONATE REABSORPTION IN THE PROXIMAL TUBULE CELL inhibited

- **Proximal tubular epithelial cells are rich in carbonic anhydrase**
  Membrane bound and cytoplasmic both are inhibited Counter transport of Na+ and H+ is inhibited Net excretion of Na+ occur.

- **Carbonic anhydrase is present in other sites**
  Eye , Gastric mucosa , Pancreas , CNS

- **CLINICAL USES: Rarely used as diuretic (limited efficacy)**

- Glaucoma (reduce aqueous humor formation) most common dorzolamide, brinzolamide.

-Prevention and treatment of Mountain sickness (decrease CSF production)

- Urinary alkalinization (uric acid and cystine)

- **TOXICITY:**

Drowsiness , parasthesias, Metabolic acidosis.

Reduction of urinary excretion rate of weak organic bases.

Renal stones (calcium phosphate salts) in alkaline urine. Calcium phosphate stones are less common than calcium oxalate stones. Causes include renal tubular acidosis (a kidney condition that with contineous urinary alkalinization).

Side effects attributed to sulfonamide moiety:

Allergic reactions ,Bone marrow depression ,Renal Lesions

OSMOTIC DIURETICS

Glycerin, Isosorbide, Mannitol, Urea

PHARMACOKINETICS

- Mannitol poorly absorbed by GI tract produce osmotic diarrhea
- Must be given I/V Route of excretion is mainly renal.

MECHANISM OF ACTION:

Major effect on proximal tubule and descending limb of Henle's loop.
Oppose the action of ADH in the collecting tubule Urine volume increases

Urine flow rate increases which decrease contact time between fluid and tubular epithelium
Increase renal blood flow

Extract water from intracellular compartments and expand extracellular volume

- **CLINICAL INDICATIONS:**
  To increase urine volume(acute sodium retention)
- Reduction of Intra-cranial pressure.
- Reduction of Intra-occular pressure.

- **TOXICITY Extra-Cellular Volume Expansion.**
- **Headache Nausea Vomiting**
  Dehydration Hypernatremia Hyperkalemia

<u>Contraindications</u>

- Severe renal impairment
- Dehydration
- Hyperkalemia

- **LOOP DIURETICS high-ceiling diuretics**

CLASSIFICATION

- **Carboxylic Acid Derivatives: Furosemide, Bumetanide**
  Phenoxyacetic Acid Derivatives: Ethacrynic acid

- **Carboxylic Acid Derivatives**
  They possess carboxyl + sulfamyl group. Some C.A inhibiting activity May inhibit HCO3 excretion to small extent.

- **Phenoxyacetic acid Derivative.**
  Do not possess sulfonamide group. Contains a ketone & Methyene group. No carbonic anhydrase inhibitory activity.

- **PHARMACOKINETICS Rapidly absorbed**
  Eliminated in kidney through Glomerular filtration and tubular secretion

- **As Diuretic:- 1. Main Mechanism: MECHANISM OF ACTION:**
  Inhibition of Na+/K+ / 2Cl- transporter by acting at the thick ascending limb of loop of Henle.

- So NaCl, K+ REABSORBTION & SECONDARY REABSORBTION OF Ca2+ , Mg2+ IN THICK ASCENDING LOOP OF HENLE inhibited.

- **2. Contributory Mechanisms:**

a. Interference with counter current multiplier exchange system.

b. Change in the renal haemodynamic state.

c Increase synthesis of prostaglandins

- **Increase calcium and magnesium excretion**
  Reduce pulmonary congestion and left ventricular filling pressure

THERAPEUTIC USES:

1.Acute pulmonary edema with LVF

2. Acute renal failure (increase rate of urine flow)

3. Refractory edema of nephriticsyndrome.

4. Refractory cases of Hypertension.

5. Hyperkalemia.

6. Hypercalcemic States

7. Acute Drug Poisoning – Forced Diuresis Anion over dosage (Bromide, fluoride,Iodide)

- **ADVERSE EFFECTS:**

I. Due to Disturbance in fluid and electrolytes balance:-

Hypokalemia,Hypochloremia,Hyponatremia,Hypocalcemi,aHypophosphatemia

II. Metabolic Adverse Effects

Hypomagnesemia level Depletion of fluid volume Hypotension Metabolic Adverse Effects Hyperuricemia- worsens gout Hyperlipidemia- LDL & cholesterol

III. Misc Adverse Effects

Ototoxicity Hepatotoxicity

IV. Allergic Reactions:

Related to sulfonamide moiety.

Skin rashes Dermatitis Photosensitivity Eosinophilia Interstitial Nephritis

- **DRUG INTERACTIONS**

Aminoglycosides, carboplatin and other agents (aggravation of ototoxicity)

Anticoagulants---- increase activity

Digitalis ---- increase arrhythmias

Lithium ---- increase plasma levels

NSAIDs blunt diuretic response

CONTRAINDICATIONS

Severe Na+ and volume depletion
Hypersensitivity to sulfonamides Anuria

- **THIAZIDE DIURETICS**

CHEMISTRY Sulfonamides derivatives Structural analog of 1,2,4 – benzothiadiazine- 1,1- dioxide

CLASSIFICATION OF THIAZIDES

DURATION OT ACTION BASED

I. Short Acting 6-12 hrs Chlorothiazide, Hydrochlorothiazide, Hydroflumethiazide, Bendrofluzide

II. Intermediate Acting

Cyclothiazide12-24 hrs, Quinethazone18-24 hrs
Methylclothiazide24 hrs

III. Long Acting

Indapamide 24-36 hrs

Polythiazide 24-40 hrs
Chlorthalidone 24-74 hrs

- **PHARMACOKINETICS All can be administered orally**

Chlorothiazide is the only diuretic for parenteral administration

Chlorthalidone has longer duration of action

All thiazides are secreted by organic acid secretory system in PCT compete with secretion of uric acid.

<u>MECHANISM OF ACTION:</u>

As Diuretic

As Anti-Hypertensive

- **MECHANISM OF ACTION AS DIURETIC :**

- **NaCl REABSORPTION IN DISTAL CONVOLUTED** TUBULE inhibited (Na+ - Cl- SYMPORT INHIBITORS)

- Inhibit Na+ Cl- symport in distal convoluted tubule
- Enhance Ca++ reabsorption so Used for treatment of kidney stones caused by hypercalciuria

- **MECHANISM OF ACTION AS ANTI – HYPERTENSIVE:**

I) Initially transient fall of B.P because of diuretic effect:

Increased excretion of NaCl and water result in Decreased extra cellular fluid volume

Decreased venous return

Decreased Cardiac Output

Decreased B.P.

II) NATRIURETIC ACTION AS A MECHANISM FOR ANTI-HYPERTENSIVE EFFECT

Decreased concentration of sodium in the vascular beds as well as

loss of response of vascular smooth muscles to circulating catecholamines induce vasodilatation with fall in BP.

THERAPEUTIC USES:

- Management of Odema of :

Chronic CCF

Hepatic Cirrhosis

Chronic Renal Failure

Nephrotic Syndrome

Acute Glomerulonephritis

- Anti-hypertensive
- Nephrogenic Diabetes insipidus
- Idiopathetic Hypercalciuric states
- Osteoporosis
- Pre-eclampsia of pregnancy
- Halide poisoning (Br Intoxication)

- **ADVERSE EFFECTS:**

Due to Abnormalities of fluid and electrolyte balance:

- ❑ Extra-cellular volume depletion
- ❑ Hypotension
- ❑ Hypochloremia
- ❑ Hyponatremia
- ❑ Hypokalemia
- ❑ Hypomagnesemia
- ❑ Hypophosphatemia
- ❑ Hypercalcemia
- ❑ Decreased plasma level of halides
- ❑ Metabolic Alkalosis

- **METABOLIC EFFECTS: Hyperglycemia (Impaired carbohydrate tolerance)**

Hyperuricemia

Hyperlipidemia (increase serum cholesterol and LDL)

- **Misc Adverse Effect:**

CNS (vertigo, headache, paresthesias and weakness)

GIT (cramping ,diarrhea, cholecystitis and pancreatitis)

Allergic Reactions

Hematological Reactions

Sexual dysfunction

- DRUG INTERACTIONS of Thiazides

- diminish effect of anticoagulants, uricosuric agents, sulfonylureas and insulin.

- Increase the effects of anesthetics, diazoxide, Cardiac Glycosides, lithium.

- **Effectiveness of thiazide diuretics is reduced by NSAIDs, bile acid sequestrants, Amphotericin B and corticosteroids.**
- Increase risk of hypokalemia which increase the risk of quinidine induced arrhythmias.

- **CONTRAINDICATIONS to thiazides**

Impaired renal functions

Diabetes mellitus

Impaired hepatic functions

Impaired renal functions

Adrenal diseases

Gout

- **POTASSIUM SPARING DIURETICS (Low efficacy diuretics)**

PHARMACOKINETICS

Spironalactone is a synthetic steroid.

Inactivation occur in liver

Slow onset of action (several days)

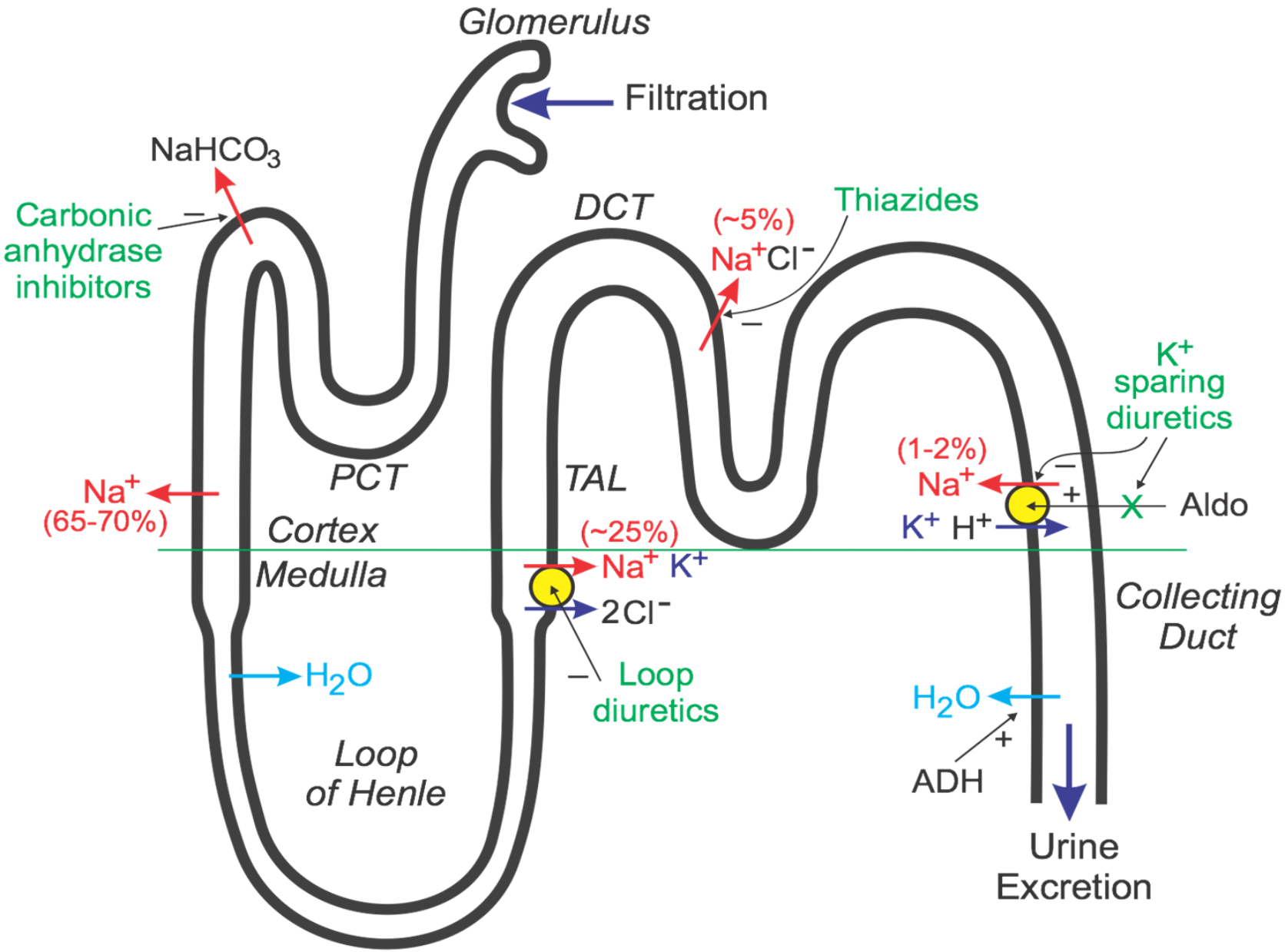
- MECHANISM OF ACTION:

Na+ REABSORBTION COUPLED TO K+ & H+ SECRETION IN COLLECTING TUBULE

Antagonize the effects of aldosterone in collecting tubules.

Inhibition of Na influx through ion channels in the luminal membrane (amiloride and triamterene)

H+ ion secretion from intercalated cells is decreased leading to acidosis.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K+ H+
X
Aldo
Na+ (65-70%)
PCT
TAL
Cortex
Medulla
(~25%) Na+ K+
2Cl−
Collecting Duct
H2O
Loop diuretics
H2O
Loop of Henle
ADH
Urine Excretion

CLINICAL INDICATIONS:

1\Primary aldosteronism

2\Secondary aldosteronism

Potassium wasting due to excess Sodium delivery to distal nephron sites (Thiazide and Loop diuretics)Used in combination with these drugs Long term treatment for refractory edema as in Cirrhosis

- **TOXICITY Hyperkalemia Hyperchloremic Metabolic Acidosis**

Endocrine abnormalities (gynecomastia)

Acute Renal Failure (triamterene)

Kidney Stones (triamterene precipitate in urine causing stones)

CONTRAINDICATIONS

Chronic Renal failure (hyperkalemia) ACE inhibitors. Liver disease , Peptic ulcer

- **Diuretic combinations**
  *Loop agents and thiazides (block Na+ absorption in all segments)

*Potassium sparing diuretics and loop diuretics or thiazides (K+ level is maintained)

THANXS