



A woman with dropsy treated by paracentesis



The Bulgarian Weightlifting Federation was sanctioned and suspended from participation in the 2000 Olympic Summer Games in Sydney



Drug testing revealed the presence of furosemide

DIURETIC DOPING

To lose weight quickly in order to compete in lower weight classes e.g. wrestling, boxing, and weightlifting

“Masking” drugs to speed the elimination of banned substances e.g. steroids



DIURETICS

ILOS

Define and classify diuretics

Identify the site of action of each class of diuretics in the nephron

Describe the mechanisms of action of diuretics

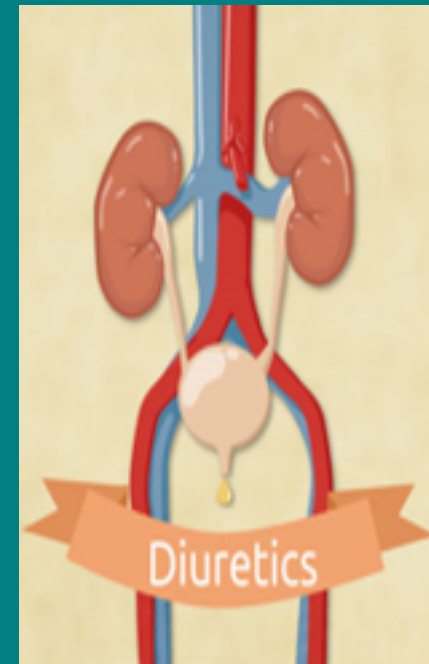


DIURETICS

ILOS

Detail on the pharmacodynamic actions and pharmacokinetic aspects of diuretics

List ADRS, therapeutic uses, contraindications and drug- drug interactions of diuretics



DIURETICS

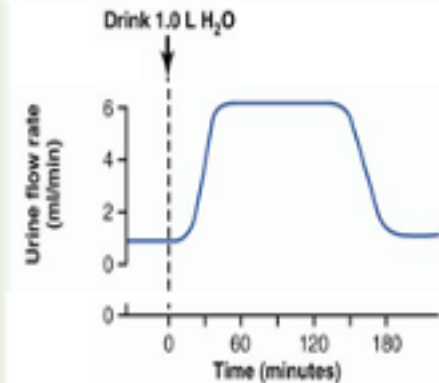
Is water a clinically-useful diuretic?

Drugs used to increase renal flow rate

- They act by \uparrow the quantity of sodium in urine (**natriuretic diuretics**)

Used to remove excess extracellular fluid (oedema)

Water diuresis



DIURETICS

The main indications

Edema of any origin

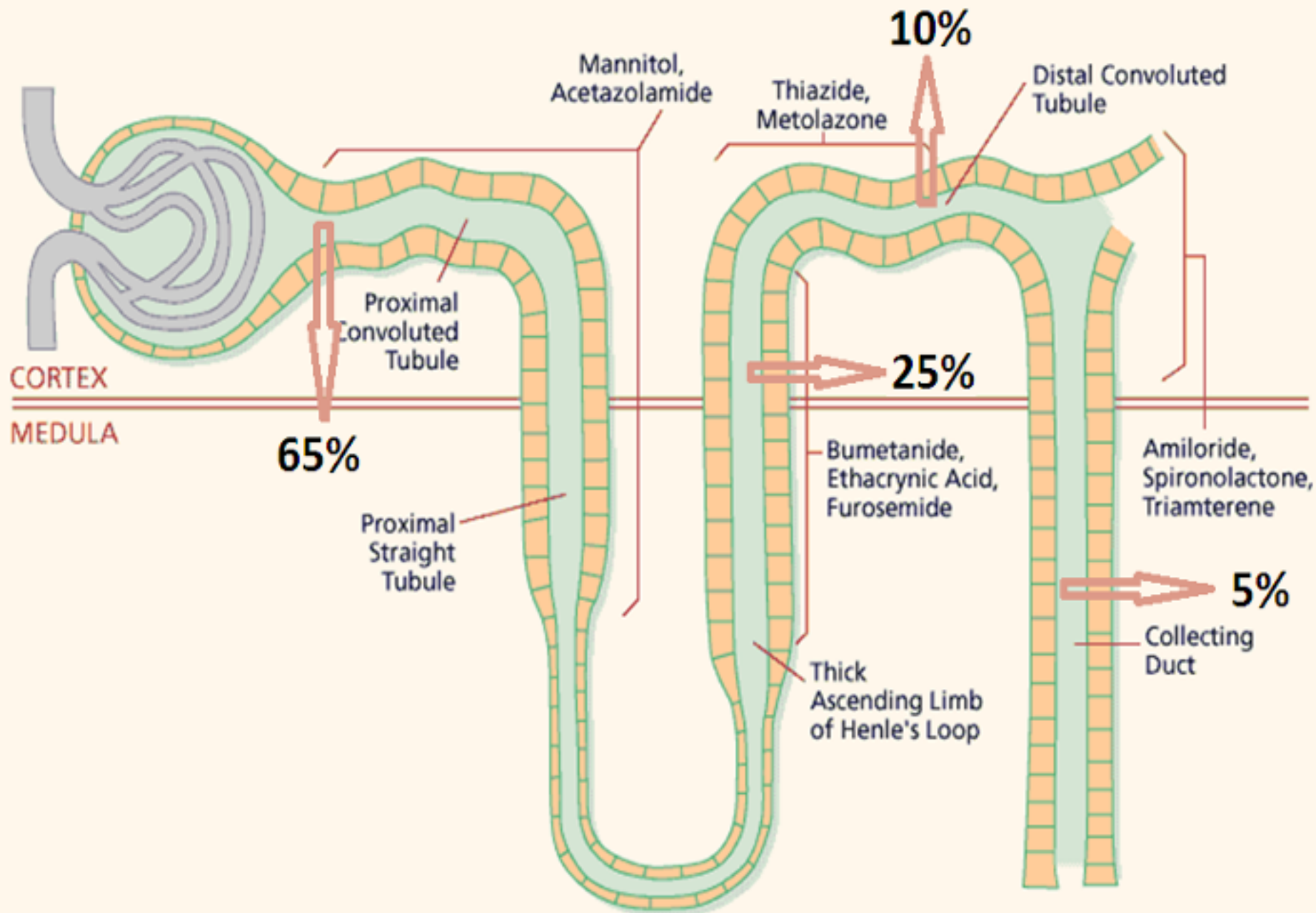
Congestive heart failure

Hypertension

Elimination of toxins



Diuretic Sites of Action



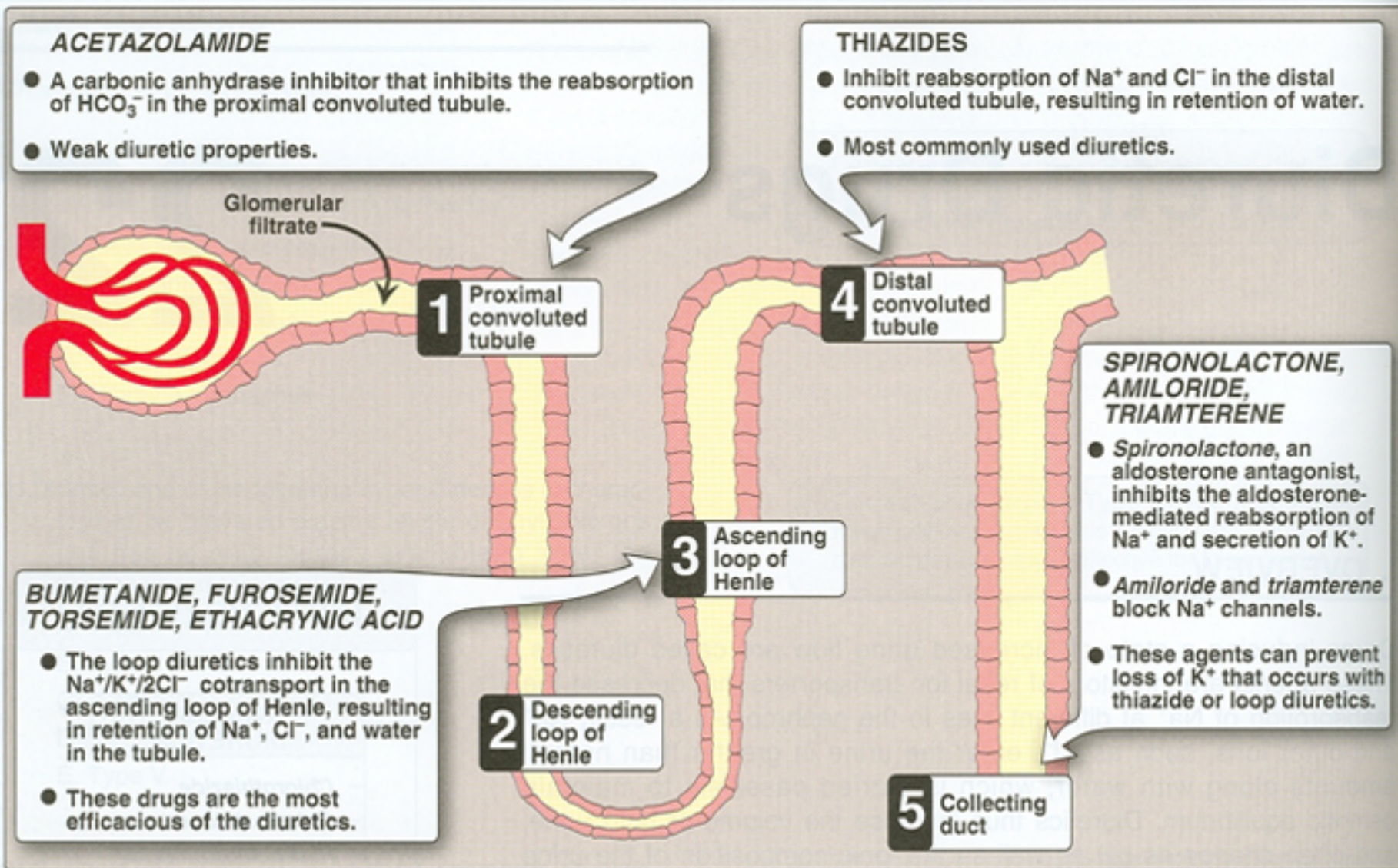


Figure 22.2

Major locations of ion and water exchange in the nephron, showing sites of action of the diuretic drugs.

Diuretics

High efficacy

Loop diuretics

Moderate efficacy

Thiazides

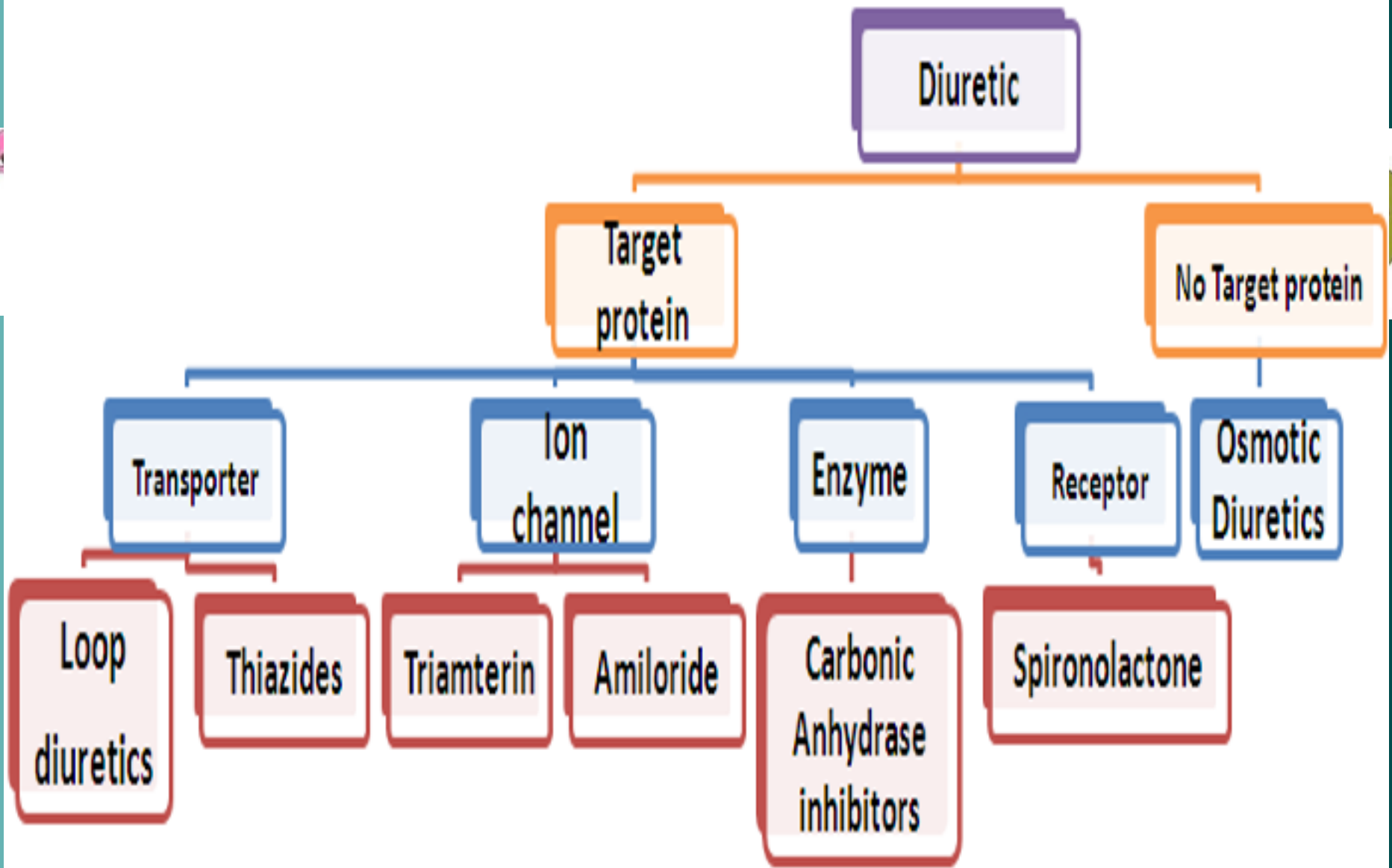
Low efficacy

K⁺ sparing

Spironolactone
Triamterin
Amiloride

Osmotic

Carbonic anhydrase inhibitors



Diuretic

Target protein

No Target protein

Transporter

Ion channel

Enzyme

Receptor

Osmotic Diuretics

Loop diuretics

Thiazides

Triamterin

Amiloride

Carbonic Anhydrase inhibitors

Spironolactone

DIURETICS

CLASSIFICATION

Action

Mechanism of action

Efficacy

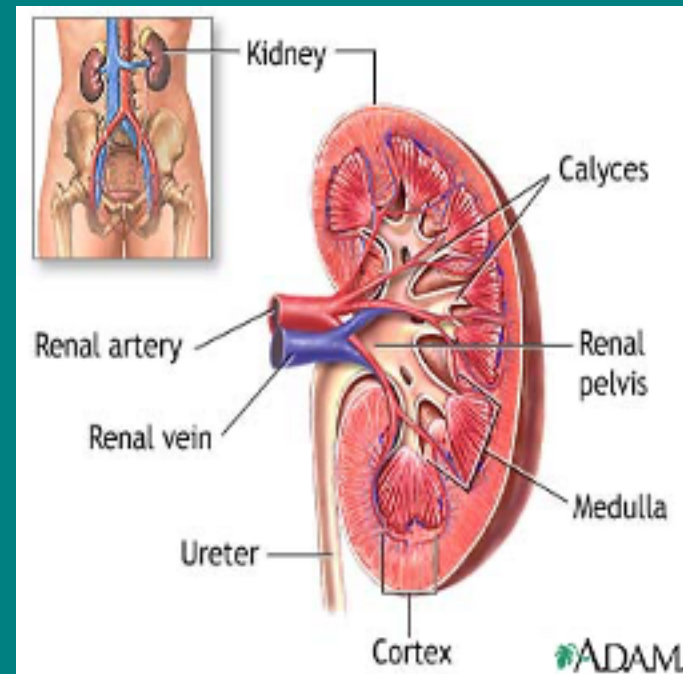
Site of action



DIURETICS I

**CARBONIC
ANHYDRASE
INHIBITORS**

**OSMOTIC
DIURETICS**

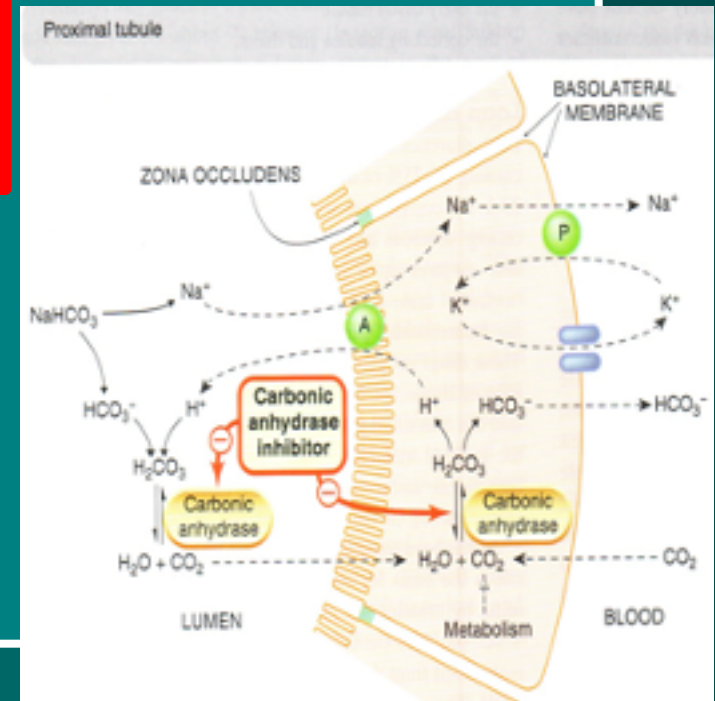


DIURETICS I

CARBONIC ANHYDRASE INHIBITORS

- Carbonic anhydrase accelerates the attainment of equilibrium in the reaction
$$\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3$$

Acetazolamide is a potent specific inhibitor of carbonic anhydrase, enzyme inhibition is non competitive



CARBONIC ANHYDRASE INHIBITORS

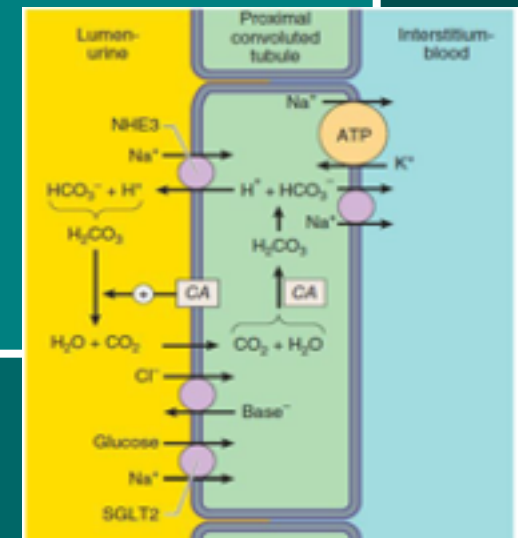
• It ↓ **reabsorption of bicarbonate** in the proximal tubule & prevent the acidification of urine in the distal tubule

• Promotes K^+ excretion by ↑ the load of Na^+ delivered to the distal tubules

• With repeated dosage the diuretic action is lost → loss of HCO_3^- & development of acidosis

• **Self-limiting action of acetazolamide** restrict its use to mild oedema .

• **Gliflozins**
X



CARBONIC ANHYDRASE INHIBITORS

PHARMACOKINETICS

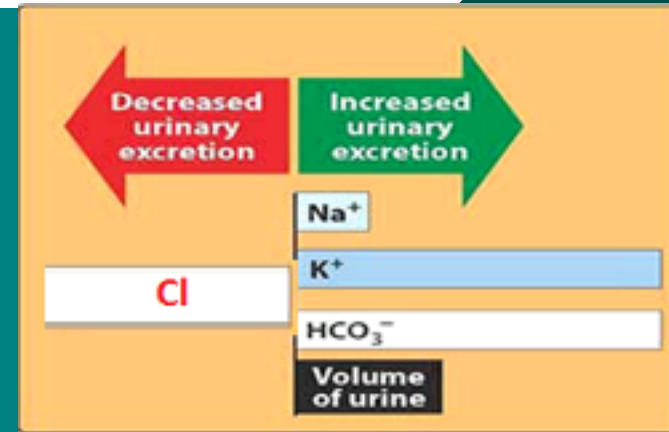
ACETAZOLAMIDE

Given orally once a day

Onset of action is rapid (30 min)

$t_{1/2}$ 6-9h

Excreted by active secretion in proximal convoluted tubules



CARBONIC ANHYDRASE INHIBITORS

DORZOLAMIDE

Is a carbonic anhydrase inhibitor

Used topically for treatment of increased intraocular pressure in open-angle glaucoma

No diuretic or systemic side effects
(Why?).



CARBONIC ANHYDRASE INHIBITORS

ADRS

Drowsiness

Numbness

Tingling sensation of the face & extremities

- Disturbance of vision

- Contraindicated in patients with liver cirrhosis (alkaline urine \downarrow excretion of NH_4^+ \rightarrow hyperammonemia & hepatic encephalopathy)

CARBONIC ANHYDRASE INHIBITORS

CLINICAL INDICATIONS

1-Glaucoma:- aqueous humor contains a high concentration of bicarbonates. ↓ of carbonic anhydrase ↓ rate of aqueous humor formation → ↓ intraocular pressure (tolerance does not develop to this effect)

2-Urine alkalinization:- uric acid, cysteine & methotrexate are relatively insoluble in acid urine. Renal excretion can be ↑ by ↑ urinary bicarbonate excretion. Effect is short lived & require bicarbonate infusion.

CARBONIC ANHYDRASE INHIBITORS

CLINICAL INDICATIONS

3-↓Formation of CSF:- ↓of carbonic anhydrase in the chorioid plexus →↓formation of CSF. Useful in management of benign intracranial hypertension.

4-Useful for correcting a **metabolic alkalosis**, especially an alkalosis caused by diuretic-induced increases in H^+ excretion & metabolic alkalosis of heart failure.

CARBONIC ANHYDRASE INHIBITORS

CLINICAL INDICATIONS

• **5-Mountain sickness prophylaxis:-** given nightly 5 days before the ascent
↓ weakness, breathlessness, dizziness, nausea, cerebral & pulmonary oedema

• **6-Adjunct for treatment of epilepsy:-** glial cells contain carbonic anhydrase. Nerves are highly responsive to rise in pH. $\uparrow 7.4 \rightarrow 7.8$ causes convulsions. \downarrow of neuronal carbonic anhydrase $\rightarrow \downarrow$ pH in the vicinity of neurons $\rightarrow \downarrow$ convulsions.



OSMOTIC DIURETICS (AQUARETICS)

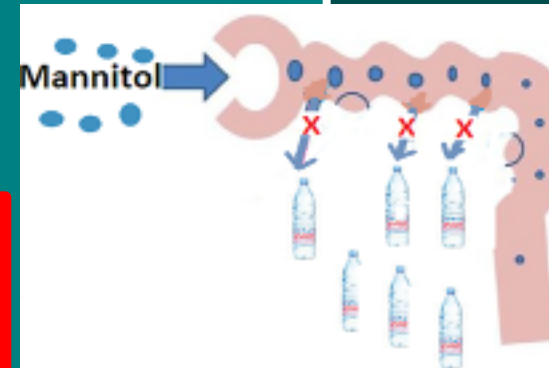
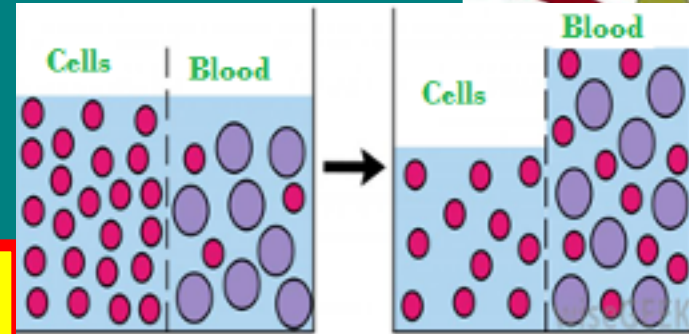
MANNITOL

In systemic circulation: Mannitol draws water out of cells into the bloodstream

Expands the extracellular fluid volume, decreases blood viscosity, and inhibits renin release, \uparrow renal blood flow

In the kidney tubules: IV administration of any solute filtered by glomeruli may produce osmotic diuresis when the amount delivered to tubules exceeds their absorptive capacity

The dissolved compound exert an osmotic pressure \rightarrow \downarrow water & Na^+ reabsorption



MANNITOL

PHARMACOKINETICS

- Mannitol, IV, not absorbed from the GIT, \uparrow water excretion with relatively less effect on Na^+ **[aquaretic]**

- If given orally \longrightarrow osmotic diarrhea

- Little metabolized

Mainly excreted unchanged in urine

Excreted by glomerular filtration

- $t_{1/2}$ 0.25-1.7h, prolonged in renal failure to 36h

MANNITOL

CLINICAL USES

1-To eliminate drugs that are reabsorbed from the renal tubules in acute poisoning e.g. salicylates, bromides, barbiturates

2-To prevent acute renal necrosis after severe injury , haemorrhage, hypovolaemia, \rightarrow \downarrow GFR, absorption of water & salts is complete , distal part dries up \rightarrow irreversible damage

MANNITOL

CLINICAL USES

3-To ↓ intracranial & intraocular pressure before ophthalmic or brain procedures

4-To maintain urine volume & to prevent anuria resulting from large pigmentation load to the kidney e.g. hemolysis, rhabdomyolysis



MANITOL

ADRS

- Headache, nausea, vomiting → hyponatremia
- Extracellular volume expansion, complicates heart failure & pulmonary oedema
- Excessive use → dehydration & hypernatraemia, (Adequate water replacement is required).



"How could I be retaining water? — I only drink beer."

MANNITOL

CONTRAINDICATIONS

Chronic heart failure

Anuric patients or patients not responding to a test dose of mannitol

