



KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
1ST YEAR, 5TH BLOCK

Carbonic Anhydrase Inhibitors and Osmotic Diuretics

4



RENAL BLOCK



Objectives :

- Define and classify diuretics.
- Identify the site of action of each class of diuretics in the nephron.
- Describe the mechanisms of action of diuretics.
- Detail on the pharmacodynamic actions and pharmacokinetic aspects of diuretics.
- List ADRS, therapeutic uses, contraindications and drug- drug interactions of diuretics.

DIURITICS

- Drugs used to increase renal flow & to remove excess extracellular fluid (water and Na) that causes oedema.
- They act by ↑the quantity of sodium in urine (natriuretic diuretics).

New terms:

Diuresis: is the process of excretion of water in the urine.

Natriuresis: is the process of excretion of sodium in the urine.

INDICATIONS

- 1-Oedema of any origin.
- 2-Congestive heart failure.
- 3-Elimination of toxins.
- 4-Hypertension.

CALSIFICATION

According to mechanism

1-Target protein:-

- a) Transporter: Loop of diuritics and Thiazides.
- b) Ion channle: Triamterin and Amiloride.
- c) Enzyme: CA inhibitors
- d) Receptor: Spironolactone

2-No target protein:-

Osmotic diuretics.

According to action

1-Directly-acting:-

-K-sparing:

- a)Aldosterone-antagonists
- b)Triamterine & amiloride

-K-losing:-

- a)CA Inhibitors.
- b)Thiazides.
- c)Loop-diuretics.

2-Indirectly-acting:-

Osmotic diuretics.

According to efficacy

1-High efficacy:

Loop of diuritics.

2-Moderate efficacy:

Thiazide.

3-Low efficacy:-

- a)Osmotic: CA inhibitors.
- b)K+ sparing.

Site of action of Diuretics

| segment | Function | transporter | Diuretics |
|-----------------------------|--|---|--------------------------------------|
| Proximal convoluted tubules | Re-absorption of 66% Na, K, Ca, Mg, 100% glucose and amino acids; 85% NaHCO ₃ | Na/H transporter, Carbonic anhydrase enzyme | Carbonic anhydrase inhibitors |
| Proximal Straight Tubules | Secretion and re-absorption of organic acids and bases | Acid & base transporter | None |
| Thick ascending loop | Active reabsorption 25% Na, K, Cl Secondary reabsorption Ca, Mg | Na/K/2Cl transporter | Loop diuretics |
| Distal convoluted tubules | Active tubular reabsorption of 5%Na, Cl, Ca | Na and Cl cotransporter | Thiazide diuretics |
| Collecting tubules | Na reabsorption K & H secretion | Na channels K & H transporter | K-sparing diuretics |

Carbonic anhydrase inhibitors

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

| | |
|------------------------|--|
| <p>Example</p> | <p>Acetazolamide: is a potent specific inhibitor of carbonic anhydrase, enzyme inhibition is non competitive.</p> |
| <p>MOA</p> | <ul style="list-style-type: none"> ✓ 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 HCO₃⁻ & development of acidosis. ✓ Self-limiting action of acetazolamide restrict its use to mild oedema e.g. oedema of pregnancy. ✓ ↑ urinary phosphate excretion. |
| <p>Kinetics</p> | <ul style="list-style-type: none"> ✓ 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. |
| <p>USES</p> | <p>A] Glaucoma:- aqueous humour contains a high concentration of bicarbonates. ↓ of carbonic anhydrase ↓ rate of aqueous humour formation → ↓ intraocular pressure-tolerance does not develop to this effect.</p> <p>B] Urine alkalinization:- uric acid & cysteine are relatively insoluble in acid urine . Renal excretion can be ↑ by ↑ urinary bicarbonate excretion. Effect is short lived & require bicarbonate infusion.</p> <p>C] Adjunct for treatment of epilepsy:- glial cells contain carbonic anhydrase .</p> <ul style="list-style-type: none"> ✓ Nerves are highly responsive to rise in pH, ↑ 7.4 → 7.8 causes convulsions. ✓ ↓ of neuronal carbonic anhydrase → ↓ pH in the vicinity of neurons. <p>D] ↓ Formation of CSF:- ↓ of carbonic anhydrase in the chorioid plexus → ↓ formation of CSF, Useful in management of benign intracranial hypertension. Used for Epilepsy</p> <p>E] Mountain sickness prophylaxis:- given nightly 5 days before the ascent ↓ weakness, breathlessness , dizziness, nausea , cerebral & pulmonary oedema</p> <p>F] Useful for correcting a metabolic alkalosis, especially an alkalosis caused by diuretic-induced increases in H⁺ excretion.</p> |
| <p>ADRs</p> | <ul style="list-style-type: none"> ✓ Hyperchloremic metabolic acidosis. ✓ Renal stone formation (calcium phosphate stones). ✓ Renal potassium wasting (Hypokalemia) ✓ Hypersensitivity reactions, bone marrow depression, skin rash. ✓ Reduction of the urinary excretion rate of weak organic bases. ✓ drowsiness, numbness , tingling sensation of the face & extremities , disturbance of vision <p>*Contraindicated in patients with liver cirrhosis (diversion of ammonia of renal origin from urine into the systemic circulation).</p> |

Dorzolamide

Is a carbonic anhydrase inhibitor

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

no diuretic or systemic side effects

Mannitol

| | |
|---------------------------|--|
| Kinetics | Given IV, not absorbed from the GIT, ↑ water excretion with less effect on Na ⁺ , Little or not metabolized, Excreted by glomerular filtration, acts in PCT and descending loop of Henle by osmosis , t _{1/2} 0.25-1.7h, prolonged in renal failure to 36h, expand ECF volume, ↓ blood viscosity, inhibit renin release, ↑ renal blood flow. Mainly excreted unchanged in urine. |
| Clinical uses | 1-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 3- ↓ intracranial & intraocular pressure before ophthalmic or brain procedures 4-Maintain urine volume & to prevent anuria resulting from large pigmentation load to the kidney e.g. rhabdomyolysis 5-For treatment of dialysis disequilibrium syndrome* |
| Adverse Effects | -Headache, nausea, vomiting -Extracellular volume expansion, complicates heart failure & pulmonary edema -Excessive use → dehydration & hypernatremia (Adequate water replacement is required). |
| Contra indications | - Chronic heart failure - Anuric patients or patients not responding to a test dose of mannitol. |

* Too rapid removal of solutes by dialysis → ↓ osmolality of extracellular fluids → water moves from extracellular to intracellular compartment → hypotension & CNS symptoms

SUMMARY

| | Acetazolamide | Dorzolamide | Aquaretics |
|--------------------------|--|--|---|
| Uses | <ul style="list-style-type: none"> • Glaucoma • Urine alkalinization • Adjunct for treatment of epilepsy • ↓Formation of CSF • Mountain sickness prophylaxis • metabolic alkalosis • hyperphosphatemia | <p>topically for treatment of increased intraocular pressure in open-angle glaucoma.</p> | <ul style="list-style-type: none"> • acute poisoning from: salicylates, bromides, barbiturates. • To prevent acute renal necrosis after severe injury , haemorrhage, hypovolaemia • To ↓ intracranial & intraocular pressure before ophthalmic or brain procedures. • To maintain urine volume & to prevent anuria resulting from large pigmentation load to the kidney. • For treatment of dialysis disequilibrium syndrome. • orally→ osmotic diarrhea. |
| Contra indication | liver cirrhosis | - | <ul style="list-style-type: none"> • Chronic heart failure • Anuric patients or patients not responding to a test dose of mannitol. |
| ARDr | <ul style="list-style-type: none"> • Hyperchloremic metabolic acidosis • Renal stone formation • Renal potassium wasting • Hypersensitivity reactions, bone marrow depression, skin rash. • Reduction of the urinary excretion rate of weak organic bases. • Drowsiness, numbness , tingling sensation of the face & extremities , disturbance of vision | <p>no diuretic or systemic side effects</p> | <ul style="list-style-type: none"> • Headache, nausea, vomiting • Extracellular volume expansion, complicates heart failure & pulmonary oedema • Excessive use→ dehydration & hypernatraemia, |

M C Q S

1-Which one of the following is a drug for open-angle glaucoma and effects topically ?

- A) mannitol
- B) Dorzolamide
- C) Acetazolamide
- D) spironolactone

2-A 57-old male developed progressive loss of his vision with sensation of pressure behind his eyes. To prevent further progression of the disease and to alleviate symptoms his ophthalmologist prescribed acetazolamide. Which of the following is a mechanism of action of acetazolamide?

- A) through osmotic effects
- B) through enzyme inhibition
- C) interacting with hormonal receptors
- D) through inhibition of ion channel

3-Of the following agents , which one is must avoided in chronic heart failure?

- A) acetazolamide
- B) hydrochlorothiazide
- C) mannitol
- D) furosemide

4-Which of the following agents decrease excretion of chloride ions?

- A) furosemide
- B) hydrochlorothiazide
- C) mannitol
- D) acetazolamide

5-A patient with a compromised renal hemodynamics was given a trial of mannitol. Which of the following is least likely to be associated with the effect of mannitol?

- A) retention of water in tubular fluid
- B) ability to be metabolized into an active metabolite
- C) capacity to be freely filtered
- D) ability to resist complete reabsorption by kidney tubules

6-A patient presented with glaucoma, and he has liver cirrhosis then which of the following drugs is contraindication :

- A) mannitol
- B) Dorzolamide
- C) Acetazolamide
- D) spironolactone

1-b. 2-b. 3-c. 4-d. 5-b. 6-c

We hope we made this lecture easier for you
Contact us for any questions or comments
Good Luck !

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