Pharmacology Team 431

Lecture :

Osmotic Diuretics and Carbonic anhydrase inhibitors

Contents :

DIURETICS

Definition:

- Are drugs that increase renal excretion of sodium and water resulting in increase in urine volume.
- Most diuretics act by interfere with the normal sodium handling by the kidney.
- How could urine output be increased ?

you can increase the urinary output by:

↑ Glomerular filtration . Or

↓ Tubular reabsorption (the most important clinically)

Purpose of Using Diuretics:

1. To maintain urine volume (e.g.: renal failure)
2. To mobilize edema fluid (e.g.: heart failure, liver failure; nephrotic syndrome)
3. To control high blood pressure.

Sites of action for diuretics

Most of them Target molecules for diuretics are specific membrane transport proteins in renal tubular epithelial cells (transporters).

Classification of diuretics

- Carbonic Anhydrase Inhibitors
- Loop Diuretics
- Thiazides
- Potassium-Sparing Diuretics
- Osmotic Diuretics

A) Diuretics that inhibit transport in the Proximal Convoluted Tubule (Osmotic diuretics; Carbonic Anhydrase Inhibitors):

1-**Osmotic Diuretics (e.g.: Mannitol)**

MOA: They are hydrophilic compounds that are easily filtered through the glomerulus with little **re-absorption** and thus increase urinary output via **osmosis**..

In another words, osmotic diuretics will exert their osmotic effects by prevent water reabsorption → ↑ water loss→ hypernatremia.(So They will not be used in cases of Na retention (eg: hyperaldosteronisim)

PK:

It Given Intravenously(I.V)

Can it be given orally?They can't be given orally , because they are hydrophilic &and they will poorly absorbed from GIT(they will cause diarrhea)

Indications:

- **to decrease intracranial pressure in neurological condition(cerebral edema).**

(because mannitol acts on periphery & will attract the fluids from the cerebrum)

- **to decrease intraocular pressure inacuteglaucoma(the same mechanism for intracranial pressure)**

- **to maintain high urine flow in acute renal failure(during shock, trauma& toxicities)**

Adverse Reactions of Manitol:

- **Extracellular water expansion and dehydration**

- **Hypernatremia due to loss more water than sodium**

- **Headache, nausea, vomiting**

-Adequate water replacement is required.

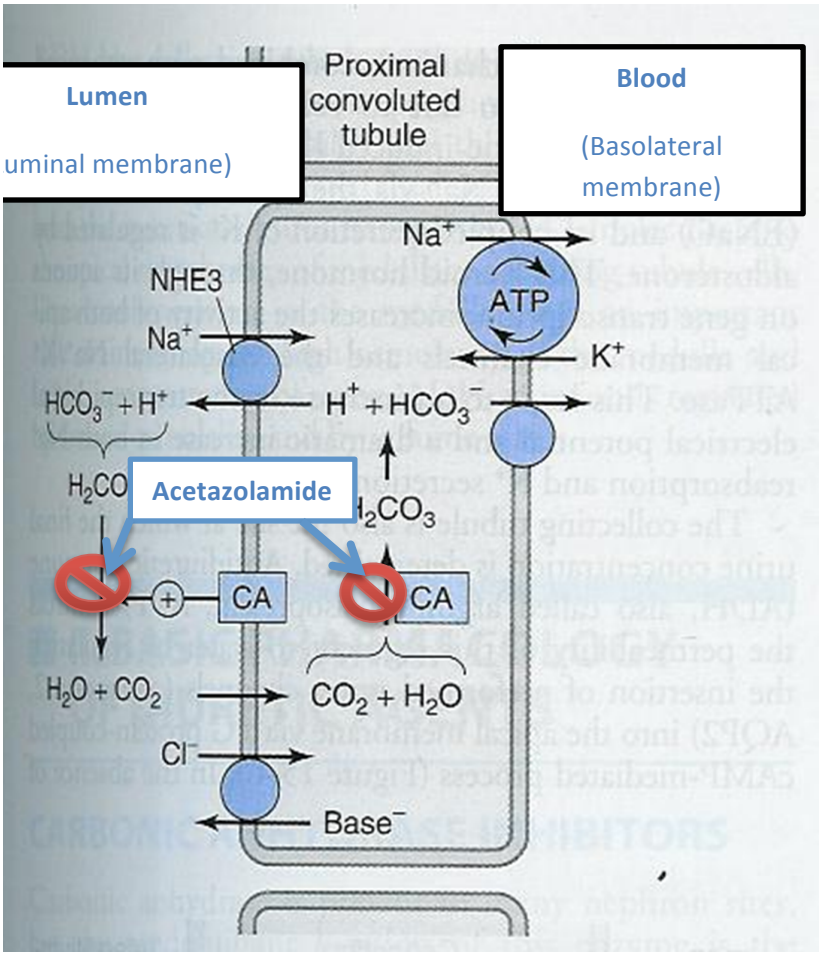
Can you conceder Osmotic Agents as good Diuretics?

No, because they cause diuresis without natriusis(Na excretion)

2. **Carbonic Anhydrase Inhibitors**

(Acetazolamide (Oral) ; Dorsolamide (Ocular) ; Brinzolamide (Ocular)

MOA:Simply inhibit reabsorption of sodium and bicarbonate by inhibiting carbonic anhydrase (on the other handthey will inhibit H^+ secretion)



Pharmacological action:

-**alkaline duresis (urine)** because increase excretion of bicarbonate ,sodium ,potassium

-increase urine phosphate (because the urine is alkalosis)

-weak diuretic -metabolic acidosis

-decrease its action after several days (self limiting as the blood bicarbonate falls) (bicarbonate is consume)

In the physiological situation:

the goal of this mechanism :The body try to reclaimHCO_3&**Na** . $HCO_3$are reabsorbed indirectly by the flowing mechanism:

Na get reabsorbed & H^+ secreted into the luminal tubule(by NA/H exchanger)

The H^+combines withHCO_3^-in the lumen to form carbonic acid (H_2CO_3)

HC2O3 are (unstable) . Hence, it is transformed by (**carbonic anhydrase CA**) into **H_2O&CO_2**

CO_2moves into epithelial cells and combines with cytoplasmic H_2O to form **H_2CO_3** (**by cytoplasmic carbonic anhydrase**)

H2CO3 cleavages into H^+andHCO_3^-.(So we restore HCO_3^-) HCO_3^- go to the ciculation

$H^+$is screted into the tubular lumen by (**NA/H exchanger**)with Na and the cycle will start again.

Mechanism of Acetazolamide and others CAIs:

Dr.Najeeb Explanation:

https://www.sugarsync.com/pf/D7431709_65906123_752522

It inhibist both luminal **CA** and Cytoplasmic **CA.** Will prevent HCo3 re –obsorbtion a. This Will lead to :acidosis of the blood (HCO_3 are the main compound that keep the PH alkaline). In addition, reduce Na level and hypokalemia.

Excreted by active secretion in proximal convoluted tubules forming alkaline urine

Side Effects:

- **Hyperchloremic** Acidosis(Due to excessive loss of HCO3 and low secretion of H^+)

-**Hypokalemia**

- **Renal Stone**(How? They cause alkalization of urine (Due to prescence of HCO_3^-) (the phosphate will loss as calcium phosphate then will deposit in the urine because its alkaline)

-**Drowsiness and parwthesia**at high doses

-metabolic acidosis

-hypersensitivity reaction (rare)

Usually, Hypokalemia are accompanied with alkalosis (except in few situations:Carbonic anhydrase inhibitors, Diarrhea….)

Contraindication:

Hepatic failuredue to decrease elimination of Ammonia.

(Ammonia get eliminated in **Acidic** urine "NH3 + H+ (in acidic medium) = NH4")

Clinical Uses of Carbonic Anhydrase Inhibitors:

- **Glaucoma**

EXTRA

- (what is the Mechanism? acetazolamide inhibits production of HCO3-. In health, it is the production of HCO3- which draws Na+ into the eye; water follows by osmosis to form the aqueous humour. In glaucoma treatment, the goal is to reduce the intraocular pressure and acetazolamide does this by reducing production of aqueous humour.)

- **Urinary alkalinization to enhance renal excretion of acidic substances (uric acid and cysteine in cystinuria)(cystinuria =genetic abnormality)**
- **Alkalization of urine??????????** and metabolic alkalosis.
- **Epilepsy;** Benign intracranial hypertension(rare)(decrease cerebrospinal fluid, CSF)
- **Acute mountain sickness (Prophylactic) (**to decrease CSF and pH of brain)
- **Hyperphosphatemia**

Side Effects of Acetazolamide:

- **Sedation and drowsness**; Hypersensitivity reaction Why?

  (because it contains sulfonamide compunds)

- **Renal stone**
- **Acidosis**; Hyperchloremia, hyponatremia and hypokalemia

Why Acetazolamide is not used as a diuretic?

Because the **compensatoey mechanism**

Dorzolamide

- **Is a carbonic anhydrase inhibitor**
- **Used topically for treatment of increased intraocular pressure in open-angle glaucoma**
- **no diuretic or systemic side effects (because it is topically**

Questions:

1-Uses of Acetazolamide include all the following except:

a.Calcium urinary stones
b.Emphysema & high altitude sickness
c. alkanize urine for secretion of salyclates
d. alkanize urine for secretion of barbuturites

2-which one of these druge can cause alkaline urine ?

a. acetohexamide
b. mannitol
c. torsemide
d. hydrochlorothiazide

3-which one of these druge can treat glaucoma topically ?
a. mannitol
b. furosemide
c. dorzolamide
d. acetohexamide

4-what is the best drug for emergncy ?
a. ksparing
b. loop diurtics
c. osmotics diuretics
d. CA inhbitors

5- mannitol may be useful in the following conditions except:

a. treatment of increased intracranial pressure
b. treatment of increased intraocular pressure
c. treatment of acute renal failure and pulmonary adema.
d. Prophylaxis in acute renal failure

Answers: Next page

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