DIURETIC DRUGS

Definition:- Diuretic drugs are drugs that induce a state of increased urine flow.

The reason for the knowledge of this group of drugs is paramount for the following reason

- A therapist or clinician should have a basic knowledge, due to the increased prevalence of urinary disorders in humans, and animals especially small animals.
- Distortion of body fluid volume could result due to a disease condition
- Distortion in equilibrium of acid-base composition or electrolytic composition
- Disorders or clinical problems of urinary origin are life threatening (problems involving the urinary system are life threatening and need immediate intervention.)

Indication of Diuretics

1. Oedema
2. Correction of specific ion imbalance
3. Reduction in the rate of intraocular fluid pressure
4. Ascites that occur due to heart failure, kidney, and liver diseases
5. Hypercalcaemia
6. Reduction of polyuria of diabetes insupidus

It is important to note:-That localized oedema, such as may occur in lymphatic or venous disorders, as in ulcerative lymphangitis, human elephantiasis could not be mobilized by diuretic therapy.

A simplified fluid and electrolytes dynamics in the nephron

- Functional unit of kidney is nephron
- It is comprised of five functional regions
- Proximal convoluted
- Descending duct
- Ascending duct
- Henles loop
- Collecting duct

Proximal convoluted;- filtration (ultra fitration0 and

(i) Reabsorption (ii) partial reabsorption

Reabsorption (complete):- glucose amino acid

reabsorption partial(Na^+, k^+, and HCO^3)

the function of proximal tubule, loop of Henle are invariant and are freely permeable to water.

Distal Convoluted tubule:- Is subjected to regulation by *aldosterone*, aldosterone is a mineralcorticoid that stimulates Na^+ / K^+ ATpase pump that activates the expulsion of Na^+ from the tubular surrounding into the interstitial fluid

It is important to note that H^+ are exchange for Na^+ under the influence of carbonic anhydrase.

Some specific points to note.

- About 16-20% of the blood is plasma filtered from the glomerular capillaries into the Bowman's capsule by hydrostatic pressure at about 120ml/minute.
- 62 liters is filtered per day in dog.
- Osmolarity of dog urine may vary from 40-2500mOsm/kg of water.
- The glomerular filtrate is 15 osmotic with plasma (290-310mOsm/L of Water).

Classes of Diuretics

This include;

The loop diuretics

Thiazides

Potassium-sparing diuretics.

The diuretics no longer in use are the *organomercurials* and the *carbonic anhydrase inhibitors.*

Others are diuretics that are low in potency this include

a. Methylxanthies
b. Aminouracils
c. Osmotic agents

Loop diuretics (high ceiling)

The loop diuretics are of highest efficacy in mobilizing Na^+ and Cl^- for this reason they are called the *high ceiling diuretic*

Chemical constituents or chemistry: they are carboxylic acids

Examples:- Furosemide

Ethacrynic acid

Bumetanide

Muzolimine

Torsemide

Furosemide:- is chemically related to thiazides it is 8-10 times more potent

Ethacrynic acid is phenol oxyacetic acid derivative and was synthesized as a sulphydrl (-SH) enzyme blocker

Mode of action

To remember their mode of action remembers their class name loop. Thus, the loop diuretic inhibit Na^{+}-K^{+} Cl^{-} Co - transportation in the thick, ascending limb of "loop of Henle" so they decrease the reabsorption of Na^{+}, K^{+} and CL^{-}

Pharmacokinetics of loop diuretic examples of these are furosemide

- After an intravenous injection
- The drug reaches its peak concentration in 30 minutes and persists for 3-6 hours
- Diuresis onset is 5 minutes after administration and persists for 24 hours.
- In oral administration, diuresis onset is 1 hour in simple-stomached animals its peak at 6-8 hours
- In cow up to 6 hours is required to obtain maximum effect in oral administration in cow.
- Furosemide is highly bound to plasma proteins. It is partially conjugated with *glucuronic acid* (20%) and is mainly excreted in urine.

Some points to note

- Bumetanide is 40-60 times more potent than furosemide., and is 100 times more potent when administered orally
- Ethacrynic acid is less potent than furosemide.

Therapeutic uses

- Required when there is need for repaid mobilization of oedema
- Cerebral oedema

- Udder oedema
- Hydrothrorax
- Ascites
- In race horses it is use to prevent exercise-induced pulmonary hemorrhages and epistaxis.

Adverse effect

Cats are more sensitive than dogs

- Fluid and electrolyte imbalances
- Hypokalaemia.
- It should not be administered with ototoxic drug (eg. Amino glycosides)

Dose - Students should find out

THIAZIDES

Chemistry:- Thiazides are heterocyclic compounds with benzene ring and an unsubstituted sulphonamide. Thiazides are the most widely used diuretics

Examples are:- Chlorothiazide
Hydrochorothiazide
Hydroflumethiazide
Cyclopenthiazide
Trichlormethiazide
Benzthiazide

To remember the examples remember the suffix *"thiazide"*

The mode of action

Inhibition of sodium, chloride, and water.

Pharmacokinetics of thiazides

- When administered orally or parenterally they well absorbed.
- They become distributed throughout the extracellular space.
- They accumulate only in the tissue of the kidney.
- Their onset of action is one hour, their duration of action varies.
- Chlorothiazide – 6-12hours

- Bendrofliazide – 24hourrs
- Their drug life in 40hours.
- They are not metabolized but are excreted by active tubular secretion.

Renal effect of thiazides

- **Increased excretion of Na^+ and Cl^-.** This occurs from the distal tubule to decrease the reabsorption of Na^+ by inhibion of Na^+-Cl symport (means co-transportation of solute species in the same direction).
- **Loss of K^+.** thiazides act proximal to the site of aldosterone-stimulated Na^+ and K^+ exchange.

  The delivery of great amount of Na^+ this, means greater exchange and loss of K^+. In exchange therefore a prolonged usage of the drug might predispose to hypokalemia.
- **Decreased calcium excretion**. The thiazides decrease calcium re-absorption of Ca^{++}. They also decrease urinary uric acid excretion.

Reduced peripheral vascular resistance

There is a reduction in blood pressure resulting from decrease in blood volume. But this later normalizes to recovery, but prolonged usage might cause hypotensive effects.

Note:- For this reasons thiazides are given concomitantly with anti hypertensive drugs like *reserpine, hydralazine, nifedipine and veratrum*

Therapeutic uses

The least three members of the group are used chlorothizide, hydro-chlorothiazide, and bendrofluazide.

- **Oedematous states**

1. milder case of oedema.
2. parturent udder oedema in cows and goats
3. cardiac and nephritic oedema.
4. bowel oedema of pigs
5. post operative and non-specific oedema due to trauma.

- **Salt poisoning/pseudocyesis.**

Thiazides are indicated to hormonal therapy to inhibit lactation, especially in pseudocyesis.

- **Hypertension** have long been the mainstay of anti hypertensive medication in humans
- **Diabetes insupidus** (di):- thiazides have the unique ability to produce hyper osmolar urine. Paradoxically they have been used to treat di of renal origin

Read dose of variousThiazides used in vet-medicine

Potassium-sparing diuretics

Examples spironolactone, triamterene, and amiloride are weak diuretics when used alone, causing only 1-2 percent of filtered sodium load to be excreted.

They act in the distal tubule and oppose the potassium excretion promoted by aldersterone. They can thus help to ameliorate potassium loss caused by more patent diuretics. Hydrochlorothiazide and amiloride; are combined examples co-amiloride

Spironolactone

Spironlactone, a synthetic steroid lactone is a competitive antagonist of the mineralocerticoid aldesterone. It interferes with aldesterone-mediated Na^+- K^+ exchange at the late. Distal tubule, increasing Na^+ loss while decreasing K^+ loss.

Pharmacokinetics

- Spironolactone is well absorbed orally, but undergoes entero-hepatic circulation.
- Its onset of action is show, and effects occur with in 48-72 hours.
- It is highly protein bound to plasma proteins but rapidly metabolized in the gut.

Uses of spironolactone

- It is indicated for treating oedema of congestive heart failure.
- Oedema resulting from primary hyperaldosteronism.
- It used as an adjunct to either thiazide or a loop diuretic to counter excessive K^+ loss.

Adverse effects of spironolactone.

- Hyperkalemia
- Gastrointestinal disturbances
- Spironolactone chemically resembles sex steroids. It has oestrogenic side-effects and may induce gynaecomastia.

- Impotence in males and menstrual irregularities in females.

TRIAMTERENE AND AMILORIDE

Mechanism of action

It inhibits active Na+ reabsorption in the distal and collecting tubules, resulting in decrease in Na^+ - K^+ exchange, hence a decrease in K^+ loss.

Pharmacokinetics of Triamterene and amiloride

- It is well absorbed after oral administration.
- Its diuretic effect could be felt for 10 hours.
- Amiloride on the other hand is poorly absorbed orally only quarter of the oral dose in absorbed but it is 10 times more potent than triameterine.
- Amiloride is not bound to plasma protein and not metabolized. The maximum effect occurs about 6 hours after an oral dose, and the plasma half-life is 10-20 hours.

OSMOTIC DIURETICS

The osmotic diuretics are not much in use in veterinary practice.

- They are small molecular weight substances.
- The filtered by the glomerular but not, reabsorbed by the renal tubules, this increase osmolality of the tubular fluid. Because the proximal tubule and the descending loop are freely permeable to water.

  Examples: *mannitol, urea, glycerol, isoserbide*.

They are therapeutically used

- In rapid reduction of intraocular pressure in glaucoma.
- To reduce the pressure and volume of cerebrospinal fluid and hence decrease in intracranial pressure in neuro surgery
- Mannitol could be administered
- It is not absorbed orally.
- It pharmacological inert and could be given in large quantity.