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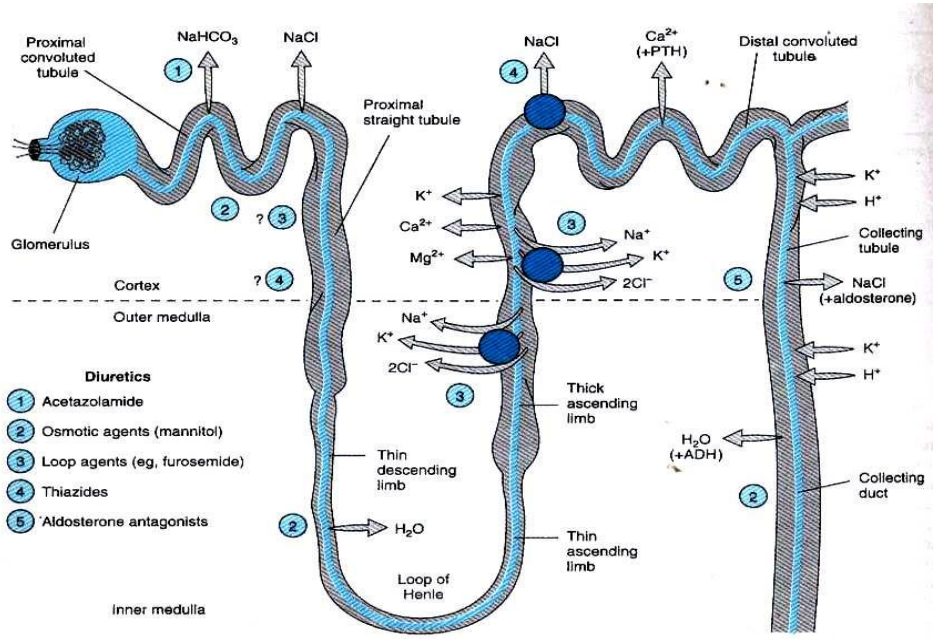
Renal Pharmacology

- The structures of the urinary system include paired kidneys, paired ureters, a single urinary bladder, and a single urethra.
- Inside each kidney are millions of individual structures, called *nephrons* that do the actual work of the kidney.
- A nephron consists of a glomerulus, Bowman's capsule, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and a collecting duct .



The main drug categories of Urinary system that involved in Veterinary practice are:

Diuretics :-

- Diuretics are drugs that increase the volume of urine excreted. Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of Na+ at different sites in the nephron.

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Major clinical uses of diuretics

1- Edema due to heart failure, nephrotic syndrome, and hepatic cirrhosis.
2- Hypertension: Low doses of a thiazide diuretic are usually used.
3- Acute renal failure: A loop or an osmotic diuretic.
4- Hypercalcemia: Loop diuretic with saline infusion.
5- Hypercalciuria: Thiazide diuretic.
6- Glaucoma: acetazolamide and dorzolamide.
7- Mountain sickness: acetazolamide.
8- Hypoventilation in COPD: acetazolamide.
9- Acute Brain injury**:** Mannitol.
10- Diabetes insipidus: Thiazides.
11- Anion overdose : loop diuretics.

Diuretics are categorized in:

- ## Thiazides and Thiazide-like diuretics:

  - Act directly on the renal tubules to block sodium reabsorption and promote chloride ion excretion.

Mechanism of action and effects:

- They act at the luminal surface of the early diluting segment of DCT and early collecting duct to inhibit the Na+/Cl- cotransporter.
- They achieve a maximum natriuresis of about 5-8% of the filtered Na+ load with a longer duration than loop diuretics.

Clinical indications:

1- Hypertension.
2- Congestive heart failure.
3- Renal stones due to idiopathic hypercalciuria.
4- Nephrogenic diabetes insipidus.

- **Side effects** include hypokalemia and cardiac dysfunction.
-**Examples** include :- **Hydrochlorothiazide, Chlorothiazide, Hydroflumethiazide,** and **Bendroflumethiazide.**

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• Loop diuretics:

-Influence the reabsorption action at the loop of Henle, resulting in tremendous diuresis**.**

- they are divided in two groups according to chemical structure :-

1. Sulfonamide structure :-
   e.g. Frusemide (Lasix) , Bumetanide
2. Sulfhydral agents :-
   e.g. Ethacrynic acid . these drugs given orally and parenteral .

Mechanism of action and effects

- They act after they are secreted into the kidney tubule by the proximal tubule anion transport mechanisms.
- They bind to the Na+/K+/2Cl cotransporter complex at the luminal border of the thick ascending limb of the loop of Henle and inhibit Cl- reabsorption.

Clinical indications:

1- Acute pulmonary edema of congestive heart failure.
2- Acute renal failure.
3- Anion overdose as bromide, fluoride, and iodide.
4- Marked edema due to congestive heart failure, nephrotic syndrome, and liver cirrhosis.
5- Hypercalcemia.

Adverse effects:

1. Ototoxicity: Hearing can be affected especially if used in conjunction with aminoglycosides. Vestibular function is less likely to be affected.
2. Hyperuricemia by competing with uric acid for the renal secretion.
3. Acute hypovolemia, hypotension, and cardiac arrhythmia.
4. Hypokalemia and alkalosis.
5. Hypomagnesemia predisposing to arrhythmia.
6. Hypersensitivity reactions.

- An example is **Furosemide, Bumetanide, Torsemide, Ethacrynic acid.**

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• Potassium-sparing diuretics:

- Act on the distal convoluted tubules to promote sodium and water excretion and potassium retention (interfere with the $Na^+\backslash K^+$ pump that are controlled by aldosterone).

Clinical indications:

1- Primary hyperaldosteronism.
2- Secondary hyperaldosteronism caused by congestive heart failure, hepatic cirrhosis, and nephrotic syndrome.
3- Combined with thiazides or loop diuretics.

Adverse effects:

1- Hyperkalemia especially in presence of renal disease or other drugs that reduce renin angiotensin system as b-blockers, NSAIDs .
2- Hyperchloremic metabolic acidosis due to inhibition of H+ secretion in parallel with K+ secretion.
3- Gynecomastia, impotence, benign prostatic hyperplasia are reported with spironolactone by effects on other steroid receptors.
4- Acute renal failure .
5- Kidney stones: because triamterene is poorly soluble.

- Examples include **Spironolactone, Triamterene,** and **Amiloride.**

• Carbonic anhydrase inhibitors.

- Block the action of the enzyme carbonic anhydrase, which is used by the body to maintain acid-base balance.

Mechanism of action

Acetazolamide inhibits carbonic anhydrase (CA), located intracellularly and on the apical membrane of the proximal tubular epithelium. CA enzyme catalyzes the reaction of CO2 and H2O leading to H+ and HCO . The decreased ability to exchange Na+ for H+ in the presence of acetazolamide results in mild diuresis accompanied by K+ secretion resulting in hypokalemia.

Clinical indications:

1- Primary hyperaldosteronism.

2- Secondary hyperaldosteronism caused by congestive heart failure, hepatic cirrhosis, and nephrotic syndrome.

3- Combined with thiazides or loop diuretics.

Adverse effects:

1- Hyperkalemia especially in presence of renal disease or other drugs that reduce renin angiotensin system as □-blockers, NSAIDs.
2- Hyperchloremic metabolic acidosis due to inhibition of H^+ secretion in parallel with K^+ secretion.
3- Gynecomastia, impotence, benign prostatic hyperplasia are reported with spironolactone by effects on other steroid receptors. Eplerenone does not cause these problems.
4- Acute renal failure when triamterene is combined with indomethacin.
5- Kidney stones: because triamterene is poorly soluble.
- Examples; **Acetazolamide** and **Dichlorphenamide.**

• Osmotic diuretics:

- Increase the osmolality (concentration) of the urine filtrate in the renal tubules, resulting in the excretion of chloride, potassium, and water.
- Used to prevent kidney failure and to decrease intracranial and intraocular pressure.

Clinical indications:

1- To increase urine volume with limited effect on electrolyte or acid-base balance as postoperative, after accidents, or hemolysis.
2- Reduction of intracranial and intraocular pressure.

Adverse effects:

1- Extracellular volume expansion prior to diuresis.
2- Dehydration and hypernatremia due to excessive use.
- Examples include **Mannitol** and **Glycerin**.

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Urolith treatment

- ***Uroliths*** are abnormal mineral masses in the urinary system .

-Types of uroliths include: struvite, calcium oxalate, calcium phosphate, urate, cystine, and mixed.

- Each type of urolith may be treated differently and may include dietary management as well as drug treatment .

Drug categories used to treat uroliths include:

- **Urinary acidifiers:**

- Are used clinically to produce acid urine, which dissolves and helps prevent formation of struvite uroliths. Their use has declined with the use of urinary acidifying diets.

- Examples include **Methionine** and **Ammonium chloride.**

- **Urinary alkalinizers:**

- Are used clinically to treat calcium oxalate, cystine, and ammonium urate uroliths.

- An example is **Potassium citrate**.

- **Xanthine oxidase inhibitors :**

- Decrease the production of uric acid, which helps decrease the formation of ammonium urate uroliths.

- An example is **Allopurinol.**