

METHYLYXANTHINES

Examples; theophylline, theobromide, other examples caffeine.

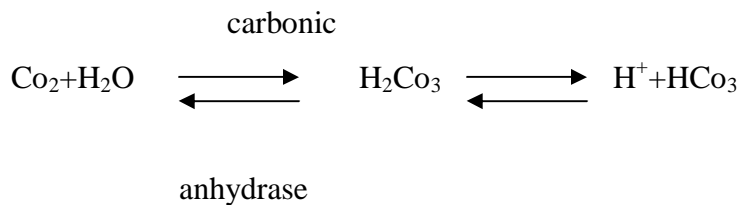
- The class of drugs has mild diuretic action due to the direct impact on the smooth muscle relaxation.
- Direct inhibitory effect on salt reabsorption in the proximal tubule.
- Theophylline is the most potent, but theobromine can be given in very large dose without producing cerebral stimulation; it is also irritating to the gut.

Amino uracils.

- They are related to the xanthines.
- They are synthesized.
- Example – aminometradine, dyphylline chlorazaniil
- The potency of xanthines and amino uracils is much less than thiazides.

Carbonic anhydrous inhibitors

Carbonic anhydrase is present in the nephron sites, especially in the luminal membrane of the proximal tubule where it catalyses the reversal of carbon dioxide to carbonic acid, this is spontaneously ionizes to hydrogen and bicarbonate ions.



So, the carbonic anhydrase inhibitors inhibit these enzyme thus reduces the availability of H⁺ generation is reduced.

HCO³⁻ is lost in urine with marked elevation in urinary pH.

The loss of HCO³⁻ causes hyperchloraemic metabolic acidosis and decreased diuretic efficacy following several days' therapy.

Examples are acetazolamide, methazolamide, ethazolamide.

Therapeutic uses

- Intraocular pressure of open angle glaucoma.

- It also decreases the production of aqueous humour probably by blocking the carbonic anhydrase pathway of the ciliary body of the eye.

Read doses and write doses of carbonic anhydrase inhibitors.

In comparison with thiazides and loop diuretics, carbonic anhydrase inhibitors are less efficacious.

URINARY TRACTS ANTISEPTICS

Urinary tract infections such as;

- Uncomplicated acute cystitis.
- Pyelonephritis.
- Urethral syndrome
- Prostatitis (these are acute infections).

Urinary tract antiseptics are totally synthetic and they exert anti-bacterial activity in urine.

They are 90% bound to plasma proteins.

The use of urinary antiseptics is in chronic urinary tract infections.

The infection of *E.coli*, other *coliforms streptococcus*, *proteus*, *pseudomonas* commonly used urinary tract antiseptics are nalidixic acid, oxolinic acid, floroquinolones e.g. profloxacin, enrofloxacin, norfloxacin, pefloxacin of loxacin, enoxacin, fleroxacin, methenamine mandelate.

GASTRO INTESTINAL DRUGS

Drugs that exert useful effects on the Git modify mainly various mechanisms that control secretion and motility. Such drugs may be grouped as:

- Appetite Stimulants
- Sialogogues
- Anti Sialogogues
- Gastric stimulants
- Gastric Sedatives
- Ulcer-healing drugs
- Emetics
- Anti- emetics
- Laxatives

- Purgatives
- Ruminatorics
- Muscosal Protectants: (Carminatives, antizmotics astrigernts)

Appetite stimulants

- Feed intake is regulated by regulatory mechanism
- There is long-term and short-term regulatory mechanisms.

The long term mechanism regulates storage of nutrients in the body, while the short term regulates the appetite. The feed intake is regulated by the satiety center located in the ventromedial-hypothalamus. While the hunger center is the lateral hypothalamus. Inappetance or anorexia is common in disease states, manipulation may delay recovery and the animal may worsen.

Sialogogues

The loss of appetite that is often associated with disease can be treated by stimulating the taste buds on the tongue. There increasing the flow of saliva. These are termed sialogogues (or Sialics) older sialogogues are known as the bitters and are derived from plants derived compounds containing alkaloids e.g. gentian powder, ginger, capsicum, strychnine and brucine (from nux vomica) and quinine (from cinchona).

The drugs used as stimulants especially in monogastrics include B-complex, vitamins, glucocorticoids, anabolic steroids, benzodiazepines, cyproheptadine and zinc.

Glucocorticoids: Increase gluconeogenesis and antagonize insulin for an overall hyperglycaemic effect. The drug acts by stimulating the appetite of well being (euphoria) examples Prednisolone, dexamethasone. Continued use of glucocorticoid has catabolic effect; skeletal muscle and collagen protein are broken down to provide the precursor for gluconeogenesis other anabolic steroid associated with stimulation of appetite are stanozolol. Boldenone are synthetic derivatives of testosterone. Megestrol acetate a synthetic progestin also stimulates appetite especially in cancer patients and cachexia and could be used in dog and cats.

Benzodiazepines: (e.g. diazepam, oxazepam, elfazepam) are effective appetite stimulant in cats, cattle and sheep (but not dogs). The drug acts via the GABA activity by increasing GABA. Elfazepam is used in sheep and cattle.

Cyproheptadine: is an antihistamine with anti serotonin action, it promotes appetite by inhibiting 5-HT receptors which control satiety.

Zinc: is an essential for sensation of taste and the response of zinc supplements is often excellent, probably by suppression of satiety centre. Meat and meat extracts and provision of small amount of highly palatable, warm bland food e.g. (one part boiled or ground meat 4 part cooked rice)at frequent intervals could stimulate appetite in carnivores.

Dose of appetite stimulants

Prednisolone	1mg/kg P.O every other day
Stanozolol	0.25-3mg P.O once a day or 2-10mg/kg I.M, once weekly.
Diazepam	Cats: 0.05-0.4mg/kg I.M or I.v or 1mg/kg P.O once a day
Cyproheptadine	Cats: 1-4mg P.O, twice a day
Megestrol acetate	Dog: 5mg/kg P.O once a day
Dried yeast	Dog: Cats 8-15mg P.O once a day.

Appetite Suppressant

They are also called anorexiant, anorexigenic agents. They may be used as adjunct to proper diet and exercise.

Mechanism of action: They are stimulants of the cerebral hemispheres of the brain e.g. Pexotroamphetamine, Chlorphentermine

Indication: In obese animals.

Antisialagogues

Inhibition of salivary secretion is achieved by administering anti muscarinic drugs. Such as atropine, hyoscine (scopolamine), and hyoscyamine, which blocks cholinergic muscarinic receptors and decreases gastro intestinal motility and secretion others agent that reduce salivation are alum which will reduce it by astringent property. Kaolin would reduce saliva flow mechanically. These are not of any value in ruminants because secretion of considerable quantity of saliva is controlled by sympathetic nervous system and therefore muscarinic blockers are less effective in these animals.

Purgatives

The term laxative, aperient, cathartic, purgative and evacuant are synonymous. These are medicines that promote defecation largely by reducing the viscosity of the contents of the lower colon. They are classified as follows:

- Irritants (or stimulants)
- Stool bulking agents
- Osmotic laxatives and fecal softeners the (emollients).

Purgatives or Cathartics exert stronger action resulting in more fluid evacuation. These drugs in low doses act as laxatives and in higher doses acts as purgatives.

Indications

Clinically, laxatives are commonly used for relief of acute non dietary constipation or intestinal impaction.

- Removal of poisons from gut
- Prevent tenesmus in advanced Pregnancy or in Prolapse.
- Evacuation for surgery or radiography.
- To soften faeces after intestinal or anal surgery.
- Constipation or intestinal impaction
- Constipation

Irritant or stimulant laxatives

Vegetable oils, aloe, Senna, cascara, Sagraads, rheum.

Mechanism of action: Increasing water and electrolytic secretion by the gut mucosa and by increasing Peristalsis. This is done possible by the enteric nerves.

The vegetable oils (Castor, Linseed and olive oil) are hydrolysed by pancreatic lipases in the small intestine to irritating fatty acids (ricinoleic acid, linoleic acid and oleic acid) horses following ingestion of castor oil, mineral oil and vegetable oil such as cotton, seed oil, groundnut oil. Other examples include: Danthron, Phenolphthalein and bisacodyl

Bulk and osmotic laxatives

When given orally it is hydrolysed to ricinoleic acid and glycerol. Ricinoleic acid is an active Cathartic; it is poorly absorbed with an onset of action of 2-6 hours.

It is not used in ruminants

Vegetable oil

A side product of vegetable oil is glycerol and has a mild stimulant effect on the rectum when administered as a suppository. In addition some of the oil that escapes hydrolysis acts as a stool lubricant. Passage of a soft oil stool generally occurs within 4-8 hours in small animals and 12-18 hours in Cascara Sagrada (Sared bark), oleo these contain glycoside that are hydrolysed in large intestine to yield irritant anthraquinones, also called emoclins. They stimulate smooth muscle and increase colonic motility. Senna obtained from pods of *Cassia- acutifolia* contains sennosides A and B

Pharmacokinetics

Anthraquinone laxatives essentially are Pro-drugs following oral administration pass to the colon where bacteria liberate the active anthrol form, which either acts locally or it's absorbed into circulation, excreted in bile to act on the small intestine thus they use 6-8 hrs to elicit their effect.

Indications

Used in acute constipation in small and large animals

Care must be taken in dams because if this is excreted in milk it may produce purgation in the young. The cathartics of choice are magnesium sulphate (Epsom salt). Magnesium hydroxide (milk of magnesia) and Sodium Sulphate (Glaubers salt).

Osmotic laxatives include sugars alcohols lactulose, glycerin, Sorbitol and Mannitol.

Magnesium Sulphate

The most used in animals and birds; it is isotonic in 3.5 percent solution orally.

Dose: 0.25-1gm/kg in horses, cattle, pigs and sheep.

Mg(OH)₂ as a 7-8.5 percent aqueous solution has a similar action to magnesium.

Horses	1-4l
Dog	5-10ml
Cat	2-6 ml

Sodium Salts

(Sulphate, Phosphate, Potassium tartrate) are also effective as saline laxatives. Sodium sulphate is the most effective saline bulk Cathartic on a molar basis. It has been used widely in horses as Carlsbad salt.

A mixture of 5 parts sodium sulphate, 2 parts sodium carbonate and 1 part sodium chloride. It is less toxic than magnesium Cathartics following absorption. Sodium Potassium tartarate (Rochelle salt) used as 5-7.5 percent solutions is relatively pleasant tasting.

Adverse effects

- Hypertonic solutions can produce significant dehydration, and must therefore, be administered with sufficient water to avoid this.
- Mg^{2+} Predispose to toxicity in patients with congestive heart failure or renal disease.
- Phosphate laxative can cause hyper phosphataemia and reduction of calcium ion

Faecal softeners (emollient)

Surface active agents that become emulsified with stool serve to hydrate and soften it and make passage easier example mineral oil, glycerin, anionic detergent, (dicotyl sodium, sulpho succinate) also called decussate sodium.

Dose of Decusate Sodium.

Cattle horses	5-15 gm
Dog, cat	15-30mg

Neuromuscular cathartics

Drugs that stimulate muscarinic receptors (e.g. arecoline, carbachol, bethanecol) or inhibit Cholinesterase (e.g. neostigmine). Increase smooth muscle activity in the gastro intestinal tract. Carbachol is a potent gastro intestinal stimulant and as such be dangerous in cases of intestinal obstruction, where rupture or intestinal intus susception can occur. Bathanecol is preferable Arecoline has been used both as a purgative and as an anthelmintic (taenicide) where intestinal stimulation assists in expelling worms. In horses is given at (dose rate of 140mg) and cattle (dose 4-33mg) The anti-cholinesterase, neostigmine has mild gastrointestinal stimulant used to treat ruminal stasis, impaction. At any urinary tract obstruction.

Dose of neostigmine

4-25mg	Dog
0.25-2.5mg	Cat

Anti-diarrhoeal drugs

Diarrhoea is the frequent passage of liquid stools. There are numerous causes including infectious agents, toxins, anxiety, drugs, e.t.c it involves increased Git motility, increased in secretion and a decrease in adsorption of fluid and thus a loss of electrolytes (Particularly Na+) and water

Classes of anti diarrhoea drugs

- Motility modifiers
- Intestinal protectant
- Adsorbent and drug that modify fluid and electrolyte transport additional to these.
- Anti microbials
- Anti inflammatory drugs
- Anti parasitic and anti toxins

Anti motility drugs

Anti – cholinergic drugs(e.g atropine, hyoscine and benzetimide) inhibit propulsive and non propulsive gastro intestinal motility. Hyoscine is utilized with an analgesic dipyrone In a parenteral formulation that appears useful in the treatment of acute intestinal spasm.

To avoid C.N.S excitement, the parasym patholytic quaternary amines such aminopentamide is opropamide, methantheline, propantheline and oxyphenonium are preferred because they do not cross the BBB readily. They inhibit normal cholinergically mediated basal secretion of the gastro intestinal tract.

Opiates

They increase smooth muscle tone and decrease peristalsis and inhibits acetylcholine release. In addition opiates directly stimulate absorption of fluid and electrolytes via U-Opiate receptors in the intestinal mucosa and C.N.S. They also have anti secretory effect. The constipating effect of morphine and codeine preclude their clinical use as anti diarrhoeal drugs. Camphorated tincture of opium (Paregoric). Oral dose rate of 1-3ml, 2-3 times a day in dogs and cats and 4-6ml/100kg of body weight, once daily in calves and foals.

Other examples of synthetic opiates Diphenoxylate, Loperamide,

Agents that modify fluid and electrolyte transport

- Non steroidal anti – inflammatory agents such as aspirin and indomethacin are effective in controlling diarrhea. Their anti diarrhoeal action is probably due to inhibition of prostaglandin synthesis. Bismuth subsalicylate is considered to be an anti –diarrhoeal.

Indication

- Acute diarrhea
- Enterotoxigenic
- *E. Coli*
- Traveler's diarrhea

Fluid replacement

Dehydration and electrolyte loss are the major causes of death in severely affect diarrhoeic young animals.

ORT(oral rehydration therapy) constitutes the following

Glucose (10.75gm/litre) or amino acid e.g. (glycine 4.5gm/l) or both these solutions contain sodium chloride, (3.5gm/l) Potassium chloride, (1gm/l) and sodium bicarbonate.

Mechanism: enhances absorption electrolytes by the enterocyte continues during diarrhea and thus helps in replacement of water and electrolyte loss.

Adsorbent and protectant

Adsorbent agents include kaolin, (magnesium, aluminum silicate) activated attapulgit (derived from wood peat, coconut or pecan shells) and pectin (carbohydrate polymer extracted from the rind of citrus fruits are insert substances that are popular for symptomatic therapy of acute diarrhea. These agent adsorbing enterotoxins or micro organism and provide a protective coating on inflamed intestinal mucosa. Kaolin pectin it is administered to animals foal, calves, swine birds lamb and kids every 4-6 hours.

Astringents

Astringents cause local precipitation of proteins on skin or mucosa membrane which provide a protective barrier for the tissue beneath. They do not penetrate cells, thus affecting the superficial layer only. Zinc, aluminum and zirconium salts have astringents actions but their use is limited to external surfaces. Intestinal astringents are tannic acid and tannin found in many plant.

Tannic acid is generally obtained from nut galls oak and tannins are found in tea, catechu, nutmeg, areca bitel(nut). They denature proteins forming protein tannate which coats and overt the bowel mucosa.

Anti microbial agents and diarrhoeal therapy

Frequently, the need arises to turn to the chemotherapy of pathogenic enteric micro-organism protozoan, and bacteria, anti microbial agents that are usually combined with one or more of the anti diarrhoeal preparation discussed above. For example Biosol M. is a combination of neomycin and methscopolamine useful in the treatment of bacterial enteric disease. Other anti microbial agents used are

- Oxytetracycline, amoxicillin,

Clavulanate- potentiated amoxicillin and trimethoprim is potentiated sulphonamides. Oxolinic acid nalidixic acid is reported to be a potentially promising drug for treatment of neonatal calf diarrhea.

Metronidazole a nitroimidazole an anti protozoal are used to treat chronic inflammatory bowel disease and colitis in dogs and cats.

Emetics

- Peripherally acting emetic
- Zinc sulphate
- Copper sulphate
- Sodium carbonate
- Ipecac

Induce emesis reflexly by stimulating sympathetic and vagal afferent receptors (i.e. sensitivity nerves endings) Pharynx and stomach mucosa.

Central Apomorphine 0.07mg/kg acting morphine xylazine.