Pharmacology of the Digestive System

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Drugs which affect appetite

Sialagogues

These are drugs which increase the volume and fluidity of saliva to improve appetite and digestion

Classification

1- Reflex sialagogues (bitters): stimulate the taste buds on the tongue so reflexly stimulate salivation. ***Bitters may be***:

a- Aromatic bitters such as orange or lemon peel.

b- Non Aromatic bitters: such as gentian, quassia, brucin and nux vomica.

2-Direct sialagogues:

- act by direct stimulation of the vagues nerve endings supplying salivary glands as (parasympathomimetics). Carbachol and physostigmine.
- **Potassium iodide** and **sodium iodide** increases saliva secretion by irritate salivary glands during its excretion and so used for dry mouth syndrome.
- **Direct appetite stimulant such as:**

Stanozolol anabolic steroid synthetic in dogs and cats.

Cyproheptadine is an antihistaminic (H1-blocker) with antiserotonin action.

Therapeutic uses:

- **To improve the loss of appetite and digestion in weak animals.**
- **To stimulate salivary production in ruminants as the maintenance of a fluid medium in rumen is essential for normal function.**
- **For atropine poisoning (dry mouth).**

Anti-Sialagogues

reduce the flow of saliva that may occur during inhalation anesthesia with ether or chloroform.

Only atropine and related alkaloids such as hyoscine and hyoscyamine have much practical value. They act by blocking the muscarinic receptors.

Oesophageal groove closure

- **Oesophageal groove** allow orally ingested fluids to pass directly from the oesophagus to the abomasum in young, milk-fed animal
- Closure of the groove is **reflexly** controlled by the autonomic nervous system.
- Failure of the oesophageal groove to close cause of bloat in milk-fed calves.
- **Atropine** will partly inhibit the closure of the groove and closure is completely inhibited by dopamine. This inhibition can be overcome by the antidopaminergic compound **metoclopramide**.

Importance of Oesophageal groove closure

Drugs may be degraded by ruminal microflora such as chloramphenicol and digitalis.

The drugs may be harmful to the microbial system such as tetracyclines, penicillins and sulfonamides.

In cattle: closure of the groove can be elicited with 60 ml of 5% copper sulphate, 5% zinc sulphate, 10% sodium bicarbonate or 10% sodium sulphate.

In sheep: 1-2% copper sulphate is effective.

Oesophageal obstruction:

in small animals, with bones or other foreign bodies becoming lodged in the oesophagus, or in cattle with pieces of root vegetable such as turnip bloat (in ruminants), due to interference with eructation.

TREATMENT WITH MUSCLE RELAXING SPASMOLYTIC EFFECT SUCH AS:

- ***Proquamezine fumarate* and *acepromazive***
- ***Xylazine* is a α2 agonist with moderate sedative and muscle relaxant properties can be used.**
- ***Hyoscine N-butyl bromide*.**
- ***Ritanserin or Ketanserin* (5-HT antagonists).**
- ***Methindizate hydrochloride*.**

III- Drugs which affect the stomach

Emetics **produce vomiting in animals having vomiting center in dogs and cats.**

The chemoreceptor trigger zone (CTZ) is a sensitive area located on the surface of medulla oblongata and connected to the vomiting center. CTZ appears to carry dopaminergic receptors, therefore dopamine can induce vomiting and the response can be inhibited by drugs with dopaminergic receptors antagonist activity.

Uses**:**

To remove a toxic material.

To remove a foreign body.

Classification

Direct (Central) emetics: stimulate the dopaminergic receptors in the CTZ which, in turn stimulates the vomiting center for dogs is:

Apomorphine hydrochloride. It is alkaloid derived from morphine, acting by stimulation of CTZ and vomiting centre. Emesis occurs 2-3 minutes after subcutaneous injection.

Xylazine

It is a potent α_2-adrenergic agonist in dogs and cats commonly causes vomiting and defecation.

Reflex or local emetics

inorganic salts such as **sodium chloride** 5%,

copper sulphate and **zinc sulphate** 1%

They produce vomiting by irritating the gastric mucosa and reflexly stimulate the vomiting center.

Mixed emetics which act both reflexly and centrally

as Ipecac syrup which has two alkaloids, **emetine and cephaline** that act locally by irritating the gastric mucosa and centrally by stimulating CTZ. It used to induce vomiting in dogs and cats after ingestions of certain toxic compounds.

Anti-emetics (Gastric sedatives)

stop vomiting in animals having vomiting centre.

Therefore, the control of emesis is desirable, or to prevent emesis due to motion sickness during animal transportation.

Anti-emetics are classified into

1- Central anti-emetics: act by depression of the vomiting center or by blocking the dopaminergic receptors in the CTZ.

a) **Metoclopramide** is a dopamine antagonist.

b) **Promazine, chlorpromazine and acepromazine**, all have sedative, antihistaminic and antidopaminergic activities.

c) **Anticholinergic agents** (parasympatholytics) as atropine, scopolamine and hyoscine.

e) **Ondansetron** is a specific inhibitor of serotonin subtype 3 receptors.

2-Local anti-emetics:

act by protection of the gastric epithelium from irritation.

a) **Anti-acids** which act by acid neutralization can reduce the symptoms of gastritis. such as sodium bicarbonate. The slower anti-acids are the less soluble compounds such as calcium carbonate, aluminium silicate (Kaolin).

b) **Demulcents** which coat and protect the gastric mucosa calcium carbonate, bismuth carbonate and aluminium silicate.

c) **The topical local anaesthetics** as benzocaine and amethocaine have been used to reduce vomiting in gastritis by depressing the sensory nerve endings in the stomach and so prevent the transmission of impulses to the vomiting center.

Antacids

orally to neutralize excess gastric acidity.
treatment of gastric ulcer and hyperacidity in dogs and cats. in ruminants for treatment of ruminal acidosis.

Anti-acids are classified into

Systemic (general) anti-acids:

soluble alkaline salts that may be absorbed. Their anti-acid effect is produced in the stomach before absorption and in the blood and urine after absorption.

a - **Sodium bicarbonate** which reacts with excess acid and liberate CO2 which lead to re-stimulation of acid secretion.

b- **Sodium** and **potassium citrates** which neutralize hyperacidity without releasing CO2.

Non systemic (local) anti-acids

These are insoluble alkaline salts that remain within the GIT. effect is produced only in the stomach.

a- **Calcium carbonate** and **magnesium carbonate** that neutralize excess acidity and liberate CO2

b- **Magnesium oxide, magnesium trisilicate** and **aluminium hydroxide** neutralize excess acidity without releasing CO2.

3-Histamine (H_2-receptor) antagonists:

Cimetidine ranitidine and famotidine are block gastric acid secretion from parietal cells by blocking the H_2-receptor.

4-Sucralfate:

an antiulcerative has a cytoprotective effect on GIT mucosa. It disassociates in the acid of the stomach to sucrose octasulfate and aluminum hydroxide, which polymerizes to a viscous, sticky substance that creates a protective effect by binding to ulcerative mucosa.

5- Misoprostol:

It is a synthetic prostaglandin E1 analog used in dogs to reduce ulcers**.**

Demulcents (Gastrointestinal Protective)

These are agents which are used to protect the mucous membrane of gastrointestinal tract in cases of ulcer or inflammation. Demulcents include inert, insoluble substances

1. Insoluble Salts $CaCo_3$ – Alum .Silicate
2. Sugars Honey molasses
3. Gums
4. Animal Proteins egg albumin gelatin

Carminatives

used orally aid the expulsion of excess gases from the GIT by relaxing the sphincters.

***Uses*:**

Flatulent colic.

Free gases Tympany.

Turpentine oil, peppermint, anise, eucalyptus, clove and cinnamon oils.

Antizymotics

prevent the excessive fermentation by killing or inhibiting rumen microflora, so decrease the production of gas.

They may be given by stomach tube, as a drench or injected directly into the rumen through a cannula.

Turpentine oil remains as the only volatile oil used as an antizymotic.

Treatment of tympany and frothy bloat

Tympany and frothy bloat may be caused as a result of ruminal stasis.

Carbachol is injected subcutaneously for treatment of ruminal stasis.

In case of free gas tympany, can be removed by:

- **Passage of a stomach tube.**
- **The use of a trocar and cannula.**
- **Using of carminatives and antizymotics as turpentine oil.**

Treatment of this case (frothy bloat) is by anti-frothing agents that cause a reduction in foam stability such as:

- **Polymerized methyl silicone** direct intraruminal
- **Poloxalene** orally by drench or stomach tube**.**
- **Dioctyl sodium sulfosuccinate or Detergents.**
- **Vegetable oils** such as peanut, sunflower
- **Turpentine oil** (cattle: 15-60 ml) in linseed oil by stomach tube, drench or by cannula.

Modulators of ruminoreticular motility:

anticholinergics, adrenergics, opiate analgesics, CNS depressants and (cyanide) can result in ruminoreticular Hypomotility or atony.

Treatment:

Parasympathomimetic agents such as neostigmine, carbachol .

Metoclopramide

IV- Drugs which affect the intestine
Purgatives and lubricants

A purgative stimulate of intestinal motility and results in the expulsion of intestinal content from the colon and rectum.

A lubricant only helps normal defecation without increase in the intestinal motility.

***Uses*:**

1. In constipation not to mechanical obstruction.
2. In simple diarrhea due to putrefaction.
3. To remove a toxic material.
4. After anthelmintics to help the expulsion of dead worms

1- Lubricants (laxatives)

Lubricants have an oily property and produce a laxative effect only.

liquid paraffin act mechanically, once administered, It coats the intestinal mucosa and contents, and so help the passage of faecal material.

Its disadvantage is retardation of food absorption and interference with absorption of fat-soluble vitamins (e.g. vitamin A, D and E).

2-Bulk purgatives:

The members of this group increase in volume of the intestinal contents. This increase causes distension of the intestine which induce a reflex contraction of intestinal musculature by stimulation of the mechanoreceptors in the intestinal wall and an increase in power and speed of peristalsis.

Simple bulk

Agar agar, methyl cellulose, and **wheat bran**

These substances are resistant to digestion in the GIT absorb water, swelled forming gelatinous masses and themselves increase in bulk in small animals particularly when sharp foreign bodies (needles, sharp bones and stone) have been swallowed.

Lactulose, is a disaccharide (galactose/fructose) hyperosmotic cathartic that is not hydrolyzed by gut enzymes but metabolized in the colon. It increase osmotic pressure causing a laxative effect and used in cats

Saline bulk

hypertonic solutions of **magnesium sulphate and sodium sulphate** their ability to raise the osmotic pressure in the intestine as they are highly lionized & slowly absorbed so withdraw water from the tissues into the intestinal lumen. They are most suitable for ruminants.

- Purgation occurs after 3-12 hours in simple-stomached animals and 18 hours after dosing in ruminants.

Irritant purgatives

They act by irritation of mm of the intestine.

***a) Direct irritant purgatives*: Caster oil, Linseed oil** and **phenolphthalein**.

Caster oil is hydrolyzed in intestine by bile into resinolic acid and glycerol. Resinolic acid combine with Na forming sodium resinolate which exerts a mild irritant effect. The effect is seen within 4-8 hours. A part of caster oil acts as a lubricant before hydrolysis suitable for dogs and cats

Linseed oil acts in a similar way as caster oil except that the soap formed is sodium linolinate.

Phenolphthalein possesses marked small and large intestine irritant properties.

Ph-Ph combines with Na of bile forming **sodium phenolphthalinate** which irritates the intestinal mucosa causing purgation .A part of this salt is absorbed and excreted via the bile into the small intestine causing purgation .This cyclical action may continue for 2-3 days (after an initial action with in 4-6 hours limited to the pig, dog and cat . **Bisacodyl**, increases peristalsis by direct stimulation of the intestinal smooth muscle and increase fluid and ion accumulation in large animals.

Indirect irritant purgatives

The main members of the group are the **anthracene purgatives** (**aloes, senna, cascara, rhubarb**) contain mainly **emodine** and **crysophanic acid** dissolved and absorbed then metabolized into irritant agents excreted into the large intestine, which is irritated and stimulated. Therefore, anthracene purgatives are of most value in cecal impactions of the large intestine like horses.

Neuromuscular purgatives

given hypodermically increasing the movements of the intestine. They act either by

(a) stimulating the vogues as by arecoline, physostigmine, pilocarpive, carbacol, etc… or

(b) increasing reflex excitability of Aurbochs plexus as by nux vomica

(c) stimulating directly the intestine a pitutrin, bariumchloride, etc….

Enemas

Enemas are applied for the removal of impacted rectal and colonic contents.

introduction of large volume of **warm, soapy water** or **glycerine** into rectum. The distension caused by the fluid stimulates contractions in the colon and rectum while the fluid also softens the faecal mass.

Docusate sodium and docusate calcium salts are fecal softeners that decrease surface tension and allow water and fat to penetrate the formed feces, thus softening the stool of the small animals.

Intestinal antispasmodics (spasmolytics)

reduce intestinal contractions and so remove the spasmodic colic.

***Parasympatholytics*: Atropine** and **hyoscine** are commonly used for treatment of spasmodic colic and diarrhea by blocking the muscarinic receptors of the intestinal muscle.

***Direct intestinal muscle relaxant*:** Some drugs have a direct relaxant effect on the intestinal muscle as **Papaverine, ether, chloroform** and **chloral hydrate**.

Intestinal astringents

***Vegetable astringents*: Tannic acid** and **plants** containing tannic acid as **catechu, krameria** and **kino**. The astringent action of tannic acid is rapid in onset as its conversion into inactive gallic acid is rapid. They are used in the form of powder or tincture.

***Metallic astringents*:** Both **aluminium** and **zinc salts** have astringent actions but their use is limited to external surfaces.

Adsorbants

insoluble agents that bind toxic and other undesirable substances and carry them out of the GIT without any chemical reaction. In addition, they form a coat over the enteric mucosa and protect it from irritants.

charcoal, calcium carbonate, bismuth carbonate, aluminium silicate (Kaolin), aluminium trisilicate and **pectin**.

Uses: in case of poisoning and flatulent colic.

Cholagogues:

help the flow of bile from gall bladder into duodenum by:

- Contracting the muscle of the gall bladder as by **cholecystokinin**.
- Relaxing the sphincter of Oddi as by **magnesium sulphate**.

used in case of indigestion due to less bile.

Choleretics

stimulate the liver cells to secrete more bile.

Cincophen and **bile salts** are used as choleretics

They are used to help digestion of fat in case of chronic liver diseases

Drugs affecting digestive functions

1- Pancrealipase: It contains the pancreatic enzymes lipase, amylase and protease which help in the digestion of fats, proteins and carbohydrates in dogs and cats.

2- Ursodiol: It is a naturally occurring bile acid which increases bile flow, decreases the intestinal absorption of cholesterol and protect the hepatic cells from toxic bile acids.

Treatment of diarrhea

1- Fluid therapy: I/V fluid therapy using saline solutions is only necessary in severely affected, comatosed animals. In most animals, oral fluid therapy is both effective and practical. **Glucose** and **amino acids** continue to be actively absorbed from the gut in the diarrheic animal and the process is accompanied by the absorption of sodium and water.

A typical fluid therapy may contain **glucose, glycine, sodium, potassium** and **citrate or acetate**. The inclusion of salts of weak carboxylic acids such as citrate or acetate has a dual effect.

They form a source of bicarbonate when metabolized by the liver, and they also stimulate water and sodium absorption by the intestinal cells.

***2- Antimicrobial therapy*:** The choice of antimicrobials for diarrhea is made on the basis of spectrum of activity (where Gram-negative activity is required) and characteristics of absorption (where poorly absorbed compounds are preferred). Commonly used compounds include **streptomycin, neomycin, apramycin, amoxicillin** and **oxytetracycline**.

3-Adsorbants*: *Kaolin (natural aluminium silicate): has been used as a symptomatic treatment for diarrhea. It is intended to adsorb and so remove toxins from contact with the intestinal mucosa. important toxins in diarrhea of young.

In older animals, the compound may be more effective. ***Bismuth salts***: **Bismuth carbonate** and **salicylate** are used in the treatment of diarrhea.

***4- Drugs which reduce intestinal motility*:** Intestinal hypermotility appears to be a common cause of diarrhea. This may be due to irritation of the intestinal mucosa, or to increased secretion stimulated by bacterial enterotoxins. **Antimuscarinic drugs** such as **atropine** and **hyoscine** are useful.