Lecture Notes on

Drugs acting on Different Body Systems

(Unit IV)

[As per VCI MSVE 2016 Syllabus]

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Unit IV

DRUGS ACTING ON DIFFERENT BODY SYSTEMS

Syllabus

Chapter 1 : Drugs acting on digestive system: Stomachics, antacids and antiulcers, prokinetics, carminatives, antizymotics, emetics, antiemetics, purgatives, antidiarrhoeals, choleretics and cholagogues. Rumen pharmacology.

Chapter 2 : Drugs acting on cardiovascular system: Cardiotonics and cardiac stimulants, antiarrhythmic drugs, vasodilators and antihypertensive agents, haematopoietic drugs, coagulants and anticoagulants.

Chapter 3 : Drugs acting on respiratory system: Expectorants and antitussives, respiratory stimulants, bronchodilators and mucolytics.

Chapter 4 : Drugs acting on urogenital system: Diuretics, drugs affecting urinary pH and tubular transport of drugs, ecbolics and tocolytics.

Chapter 5 : Pharmacological basis of fluid therapy.

Chapter 6 : Pharmacotherapeutics of hormones.

Chapter 7 : Drugs acting on skin and mucous membranes: Emollients, demulcents and counter irritants.

Suggested Text books of Pharmacology:

1. Veterinary Pharmacology & Therapeutics (10th Edn.-2018) – Jim E. Riviere and Mark G. Papich
2. Essentials of Medical Pharmacology (8th Edn.-2019) – K.D. Tripathi
3. Rang & Dale's Pharmacology (9th Edn.- 2019) – James M. Ritter, Rod Flower, Graeme Henderson, Yoon Kong Loke, David MacEwan & Humphrey P. Rang.
4. Goodman & Gilman's The Pharmacological Basis of Therapeutics (13th Edn.-2018) – Laurence L. Brunton, Randa Hilal-Dandan & Björn C. Knollmann.

Chapter - 1

Drugs acting on Digestive System

DRUGS ACTING ON DIGESTIVE SYSTEM

STOMACHICS

These are the drugs which promote digestion by increasing gastric secretion and motility. Examples –

(i) Agents which increase gastric secretions:

- Bitters (Gentian, Quassia and Nux vomica): These reflexly stimulate salivary and gastric secretions due to their bitter taste.
- Alkaline stomachics (Carbonate and bicarbonate salts): These cause liberation of CO_2 in the stomach, distension of stomach and acid rebounce resulting in gastric secretions.
- Cholinergic alkaloids (Arecholine): By stimulating gastric cholinergic receptors increase secretions.

(ii) Agents which increase gastric motility:

- Gastrokinetic agents which stimulate gastric contractions relax pyloric sphincter and promote upper alimentary peristalsis. Thus, these agents promote gastric emptying and passage of food into the intestine. e.g. Metoclopramide.

ANTACIDS

These are basic agents which chemically neutralize HCl present in the gastric lumen so that luminal pH is increased to an acceptable level.

Acid Rebound Phenomenon: The action of gastric antacids is usually transient and lasts only for 1-2 hours. Neutralization of acid in the stomach antrum removes negative feedback control of gastrin release, which in turn leads to elevated gastrin levels and enhanced HCl secretion. This reflex phenomenon is known as Acid Rebound Phenomenon. So, antacids must be administered frequently or with a meal to avoid this rebound effect.

The common antacids used are as follow:-

(i) Aluminium salts [$Al(OH)_3$, Al-Mg silicate and Aluminium phosphate] – Aluminium salts tend to cause constipation and are often mixed with Mg salts to prevent this side effect.

(ii) Magnesium salts [Magnesium hydroxide, Magnesium oxide, Magnesium silicate etc.]: Magnesium salts tend to be laxative and are often found in combination with Aluminium and Calcium salts. Their cathartic effects result from soluble but unabsorbed magnesium salts that remain in the intestine and retain water.

(iii) Calcium salts [Calcium carbonate]: It is a rapidly acting, potent antacid with a prolonged duration. Constipation is the potential side effect that may occur following chronic administration of $CaCO_3$.

Uses of antacids: Gastric hyperacidity, peptic ulcer, gastritis, reflux oesophagitis, chronic renal failure (uremia), ruminal acidosis (grain overload) etc.

INTESTINAL ASTRINGENTS

These are the drugs which precipitate proteins on the surface of GI mucosa and form a protective layer against the irritants. The protective layer acts as a barrier between the intestinal tissues and the irritant. They also prevent pain sensation in the intestine by protecting the exposed sensory nerve endings. The intestinal astringents are used in the treatment of diarrhoea. The common intestinal astringents are:-

- ☞ Tannic acid
- ☞ Catechu, along with ginger, chalk and creta as astringent powder in cattle.
- ☞ Aluminium hydroxide gel etc.

CARMINATIVES

These are the agents which prevent formation of gases and help in their eructation (expulsion) from the gastrointestinal tract. They have an effect of mild irritation with vasodilatation and relaxation of oesophageal sphincter, and therefore, assist in eructation process. Examples:- Oil of turpentine, powdered ginger, capsicum, peppermint oil, eucalyptus oil, anise, asafetida and black pepper.

ANTIZYMOTICS

These are the drugs used to prevent or reduce excess microbial fermentation in rumen or intestines. These are used in the treatment of bloat in ruminants and flatulent colic in horses.

Antizymotics can be given by stomach tube, as a drench or, if a trocar and canula are used, they may be injected directly into the rumen through the canula.

Dose – Cattle & Buffalo - 15-30 ml of turpentine oil + 300-600 ml of linseed oil (1:20).
Sheep & goat – 4-8 ml of turpentine + 60-300 ml of linseed oil (1:15).

Formalin can also be used as an antizymotic agent.

Dose – Cattle & Buffalo - 4 ml of formalin + 300 ml of water (1:75).
Sheep & goat – 0.6-1 ml of formalin + 100 ml of water (1:100).

EMETICS

These are agents which cause vomition in animals capable of vomition.

- ❖ Carnivores, primates, swine, certain birds and reptiles are capable of emesis.
- ❖ Horses and ruminant animals as well as rodents, guinea pigs and rabbits are unable to vomit effectively.
- ❖ Emesis may result from local stimulation of gastric mucosa by irritants; from disturbance of the vestibular apparatus (motion sickness) or may be central in

origin as in viral infections, fever, toxaemia etc. In all cases, coordination is central via the vomiting centre.

Emetics are occasionally useful to induce vomiting as a means of removal of either toxic material which has been swallowed, or to help in the removal of a foreign body which has been swallowed. Emetics are also indicated before induction of general anaesthesia if there is any possibility of food being in the stomach.

Emetics are classified as irritant and central emetics.

1. Irritant Emetics (Peripherally acting or reflex emetics):

These cause vomition by irritating the epithelium of pharynx, oesophagus, stomach and duodenum with warm water, hydrogen peroxide or saline.

A number of substances induce emesis by irritating the epithelium of the GI tract, such as – sodium chloride, sodium carbonate (washing soda) and traditional emetics, such as ipecac.

Sodium chloride is either used as solid placed on the back of the tongue, or as a solution of 1-2 teaspoonfuls in a half cup of tepid water. This usually causes vomition within 15 minutes. Orally administered H_2O_2 (3%) can also induce emesis rapidly in dogs and cats.

Ipecac syrup is an emetic commonly recommended to induce emesis in human paediatric patients. It contains the alkaloid 'emetine' which increases lachrimation, salivation and bronchial secretions. Emesis usually, but not consistently occurs as a result of both peripheral and central stimulation.

2. Central Emetics:

These cause emesis through the stimulation of dopaminergic receptors in the chemoreceptor trigger zone (CTZ). e.g. Apomorphine HCl.

Apomorphine hydrochloride is an alkaloid derived from morphine. It has the capacity to induce vomiting. Apomorphine is a dopamine agonist with intensified initial stimulatory effects (esp. that of the vomiting centre and chemoreceptor trigger zone) compared with morphine, while the secondary depressant effects are minimized. Emesis occurs within 2-3 minutes after s.c. administration and may continue for 5-15 minutes.

Approx. dosage in dogs = 3 mg s.c. or 6 mg orally (less preferable).

Xylazine is an effective sedative in ruminants and horses. In dogs and cats, its administration (1-3 mg/kg) commonly causes vomition.

ANTIEMETICS

These are drugs which prevent nausea and vomition. Antiemetics control emesis by either a central or peripheral action. Both actions depend on and can be correlated to blockade of neurotransmission at receptor sites.

There are two groups of Antiemetics based on their site of action as below:-

1. Central Antiemetics:

Centrally acting antiemetics act either by blocking the dopaminergic receptors in the CTZ (antidopaminergics) or blocking the H_1 receptors at the vestibular apparatus (antihistaminergics) and secondarily at the CTZ and emetic centre.

- **Drugs active at the vestibular apparatus:** Antihistaminics such as Cyclizine HCl, Meclizine HCl and Diphenhydramine HCl etc. have antiemetic effect and are useful in motion sickness or inner ear diseases.
- **Drugs active at CTZ:**
  (i) Metoclopramide: (Potent dopamine antagonist)
  It is used to control apomorphine induced emesis. It is 20 times more potent than phenothiazines as an antiemetic.
  Dose – 1 mg/kg orally or parenterally repeated 3-4 times daily.
  (ii) Phenothiazines: Promethazine, Promazine, Acepromazine, Triflupromazine, Chlorpromazine, Mepazine etc.
  (iii) Butyrophenone derivatives: Haloperidol and Droperidol.
  These are potent antiemetics because of their antidopaminergic activity. Droperidol is avoided in veterinary practice since it can produce behavioural side effects.
  (iv) Trimethobenzamde:
  It has been used to control vomiting caused by radiation sickness, drugs, infections, anaesthesia and uraemia. Clinically, it has not been as effective as other antidopaminergics.

2. Peripherally acting Antiemetics:

These prevent vomition by protecting the GI epithelium from irritation. Examples – Demulcents, Antacids, Protectants like kaolin, pectin and Bismuth salts.

PURGATIVES

These are drugs that promote evacuation of bowels. Strictly speaking, however, there is a distinction between laxation (the evacuation of formed faecal material from the rectum) and catharsis (the evacuation of unformed, usually watery faecal material from the entire colon).

Laxative/ Aperient	Purgative/ Cathartic
(i) A laxative has similar action as to purgatives but the effect is milder and rarely results in more than a slight intensification of intestinal activity.	(i) A purgative is a drug which causes marked intensification of intestinal activity and results in the expulsion of intestinal content from the colon and the rectum.
(ii) Milder action, elimination of soft but formed stool.	(ii) Stronger action resulting in more fluid evacuation.
(iii) A laxative action is achieved by small dosage of drugs. Few drugs only produce laxative effect no matter how large the dose. e.g. Liquid paraffin.	(iii) Large doses will cause purgation.

Classification of purgatives:

1. Lubricant purgatives
2. Bulk purgatives:-
   (i) Simple bulk purgatives
   (ii) Saline bulk purgatives
3. Irritant purgatives:-
   (i) Direct irritant purgatives
   (ii) Indirect irritant purgatives
4. Neuromuscular purgatives

1. LUBRICANT PURGATIVES or Emollient purgatives or Mechanical laxatives or Stool softeners:

Examples: Liquid paraffin, Docusate sodium (DOSS – Dioctyl sodium sulfosuccinate).

It exerts laxative action by softening and lubricating the faecal masses for easier evacuation. Lubricant laxatives may interfere with water absorption in the intestines. This type of purgation is usually preferred in the presence of prolapse of uterus, rectum or vagina, in post operative cases when straining is not desirable in advanced pregnancy and when some part of intestine is narrowed.

However, these compounds do have a number of disadvantages as well –

- In case of chronic constipation or impaction, use of these compounds decrease GI irritability which may result in further slowing of intestinal movements; thus aggravating the problem.
- Normal absorption of protein, carbohydrate, fat and essential supplements esp. fat soluble vitamins are hindered. So, continued use esp. in children is contra-indicated.
- Chronic use of these compounds may cause anal leakage (a problem in pet dogs).

2. BULK PURGATIVES:

The members of this group increase the volume of intestinal contents causing distension of the intestines, which induces a reflex countering contraction of musculature and an increase in power and speed of peristalsis.

The methods by which this increase in volume is achieved divide bulk purgatives into two groups:-

(i) Simple Bulk Purgatives:

The simple bulk laxatives are hydrophilic in nature and are not digested within the GI tract. They adsorb water, swell and increase in bulk. Examples are Agar, Psyllium (*Plantago psyllium*), Ispaghula husk (*Plantago ovata*) and methylcellulose. It is the indigestible cellulose which is responsible for water holding properties of simple bulk purgatives. These are mainly used in small animals. These are particularly useful when sharp foreign bodies have been swallowed like needles, sharp bones and stones.

Dose of agar in dog – 10 gm daily for few days.

(ii) Saline Bulk Purgatives or Osmotic Purgatives:

These consist of salts of compounds that either are not absorbed at all or are only slowly and incompletely absorbed from the GI tract. They retain or attract water into the intestinal lumen mainly by osmotic forces.

Saline purgatives are contra-indicated in dehydrated animals.

Saline purgatives affect mainly the small intestine. Those salts which are freely soluble, strongly ionized and produce two ions both of which are only slowly and sparingly absorbed are considered as good saline purgatives.

Examples –

Magnesium sulphate (Epsom salt)

Sodium sulphate (Glauber's salt) and

Sodium potassium tartrate.

Dose of Magnesium sulphate:

As purgative –	*As laxative*
Cow – 240 gm to 480 gm	Cow – 60 to 120 gm
Sheep – 60 gm to 120 gm	Sheep – 7.5 to 15 gm
	Horse – 30 to 60 gm
	Pig – 15 to 30 gm

3. IRRITANT PURGATIVES:

The irritant purgatives are those that act, atleast in part, by irritation of mucous membrane. However, it has also been shown that a number of these substances inhibit intestinal absorption of water, electrolytes and nutrients.

Example – Phenolphthalein, the anthraquinone drugs and castor oil.

Irritant purgatives are regarded as direct acting or indirect acting depending on whether a metabolic alteration is first required to form an active product.

(i) Direct Irritant Purgatives:

Examples – Phenolphthalein, Bisacodyl, Castor oil, linseed oil etc.

Phenolphthalein is a white powder, soluble in dilute alkali and used as a laboratory indicator. It possesses useful small and large intestine irritant properties. The main advantage of phenolphthalein is the prolonged period of its action and that is why it has been used in treatment of chronic constipation.

Dose – Pig – 1 to 2 gm

Dog – 30 mg to 200 mg

Cat – 15 to 65 mg.

Castor oil and linseed oil are metabolized in small intestine to ricinoleic acid and linoleic acid, respectively which possess irritant properties.

Dose – Linseed oil – Horse – 0.5 to 1.0 litre.

Castor oil – Dog – 4 to 30 ml

Foal, Calf & Pig – 30 to 180 ml.

(ii) Indirect Irritant Purgatives:

These are agents which require absorption and metabolism before substances are produced which will on excretion into the intestine, exert an irritant action and stimulate intestinal movement.

Examples – Aloes, Cascaria sagrada, Senna and rhubarb – all plant derivatives.

Cascaria sagrada - Obtained from bark of *Rhamnus purshiana.*

Senna - Leaflets of *Cassia acutifolia* and *C. augustifolia*.

Rhubarb - Rhizome of *Rheum palmatus.*

Aloes - It is the residue obtained by evaporating the liquid from the cut leaves of aloe plants – *Aloe vera, A. chinensis* and *A. perryi*.

These plant purgatives contain anthraquinone glycosides. The glycosides are not active as such. Unabsorbed in the small intestine, they are passed to the colon where bacteria liberate the active anthrol form (aglycones) called 'Emodins' which either act locally or is absorbed into circulation – excreted in bile to act on small and large intestine.

Because of this excretion into the large intestine, these anthracene purgatives are of most value in those animals which suffer from impactions of the large intestine. The horse with its numerous colon flexures and the decrease in diameter at the pelvic flexure, benefits particularly from this type of purgative. All non-ruminants respond well to anthracene purgatives. Because of this complex cycle, purgation is delayed for at least 18 hours after administration in the horse. In other animals, the actions of aloes are more rapid, although its use in other species is now infrequent.

Aloes are the drug of choice for purgation in horses.

Dose of aloes in horse – 8 to 30 gm.

Now, some synthetic derivatives of anthraquinones are also available which are more effective. 1,8-dihydroxyanthraquinone or 'dandron' is the prototype of the group.

Emodin purgatives if overdosed can cause colic and superpurgation.

4. NEUROMUSCULAR PURGATIVES:

These are cholinergic agents with muscarinic actions which initiate hypermotility of the GI tract and promote defaecation and urination. These are now not commonly used, since they are hazardous through their excessive intestinal contractions, added to severe systemic effects on the cardiovascular system.

Examples – Arecholine, carbachol, neostigmine etc.

NB: Arecholine – In addition to the purgative action, it has also anthelmintic action where intestinal stimulation assists in expelling worms.

CHOLAGOGUES

These are drugs which cause contraction of gall bladder and increase the bile flow into the duodenum by relaxing the sphincter Oddi.

Dietary fat and concentrated magnesium sulphate introduced directly into the duodenum through a tube exert a cholagogue effect through the release of CCK-pancreozymin from the upper small intestine.

Examples – Arecholine

Oxytocin

Podophyllum – Dried rhizome & root of *Podophyllum palmatus*, *P. emodi* and *P. hexandrum*.

Mercurous chloride (Calomel).

Cholekinetics – Drugs which merely cause contraction of the gall bladder.

CHOLERETICS

Substances that increase secretion of bile by the hepatocytes are known as choleretics.

A drug that stimulates liver to increase output of bile of low specific gravity (dilute bile) is called a hydrocholeretic.

Production of bile is enhanced by stimulation of vagus nerves and by the hormone secretin, which increases the water and bicarbonate content of the bile. A number of natural bile salts and several partially synthetic derivatives are used therapeutically as choleretics.

Example –

Dehydrocholic acid – It is the most potent hydrocholeretic agent.

ANTIULCER DRUGS

Peptic ulcer occurs in that part of GI tract which is exposed to gastric acid and pepsin, i.e., the stomach and duodenum.

The etiology of peptic ulcer is not clearly understood, however, it probably results from the following:-

Imbalance between the aggressive and defensive factors. Aggressive factors are acid, pepsin and *Helicobacter pylori* infection. Defensive factors are gastric mucous, bicarbonate secretion, prostaglandins, nitric oxide, innate resistance of the mucosal cells etc.

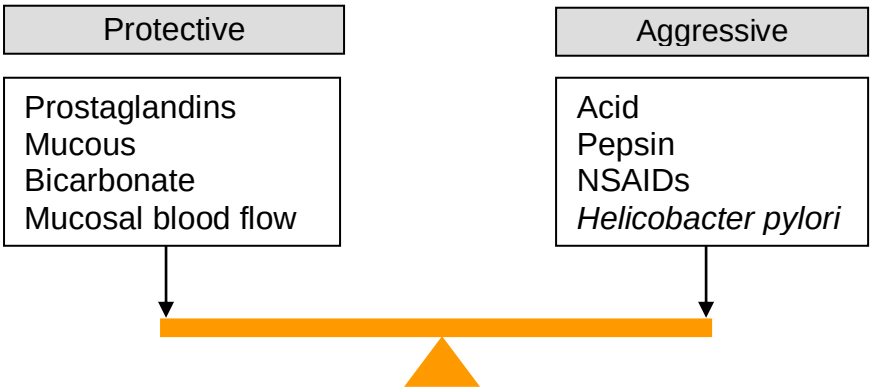

Fig.: Factors involved in maintaining acid balance.

Mucosal Defenses**:**

Defenses of the GI mucosa which act to prevent or repair GI ulceration include –

(i) Secretion of bicarbonate into the lumen and neutralization of HCl.

(ii) Secretion of a thick alkaline mucous which traps and neutralizes inward moving H^+ ions.

(iii) A gastric epithelial barrier comprising active phospholipids, a lipoprotein cell membrane and tight junctional complexes all of which prevent H^+ back diffusion.

(iv) Mucosal blood flow, which first provides nutrients and oxygen to mucosal cells and, second, removes H^+ ions that have penetrated the gastric barrier.

(v) Rapid replication of mucosal epithelial cells; and

(vi) Production of cytoprotective agents. e.g. PGE_2 (modulates HCl secretion, increases HCO_3^- & mucous production and enhances mucosal blood flow & epithelialization), sulfhydryls (act as scavengers of oxygen and tissue damaging radicals) etc.

CLASSIFICATION OF ANTIULCER DRUGS:

(I) Gastric Antisecretory drugs: (Reduces gastric acid secretion)

(i) Anticholinergic drugs: Pirenzepine, Propantheline and Oxyphenonium.

(ii) H_2 receptor antagonists: Cimetidine, ranitidine, famotidine, loxatidine etc.

(iii) Proton pump inhibitors: Omeprazole, Lansoprazole, Pantoprazole etc.

(iv) Prostaglandins: Misoprostol, Enprostil, Rioprostil etc.

(II) Cytoprotective Drugs:

(i) Antacids: Already discussed previously.

(ii) Ulcer protectants: Sucralfate, PGE_1.

(iii) Anti-*Helicobacter pylori* drugs: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline etc.

Anticholinergics**:** Despite the role of muscarinic receptors in gastric acid secretion, Anticholinergics have not proven effective for control of GI ulceration in animals. Pirenzepin, a selective M_1 antagonist has been used for peptic ulcer in Europe.

H_2 receptor antagonists: These are reversible, competitive antagonists that reduce gastric secretion of both HCl and pepsin, induced by a variety of secretagogues.

e.g Famotidine – Most potent (32 times more potent than cimetidine)

Ranitidine – 5-12 times more potent than cimetidine.

Proton pump inhibitors: These drugs are potent antagonists of H^+, K^+–ATPase proton pump, the final step in gastric acid secretion stimulated by any antisecretagogue.

Omeprazole is 30 times more potent than cimetidine.

Prostaglandins:

PGE_2 and PGI_2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucous + HCO_3^- secretion.

PGE_1 (Misoprostol) is an antisecretory, is also a cytoprotectant. In addition to controlling HCl secretion, it increases mucous and HCO_3^- secretion and enhances epithelialization of the mucosa and mucosal blood flow. It helps to treat GI damage associated with NSAID therapy.

Sucralfate:

It is an orally administered disaccharide (sucrose) aluminium hydroxide product which binds to and protects the ulcerated site from acid, bile and pepsin activity.

Anti-*Helicobacter pylori* agents:

Helicobacter pylori is a Gram negative bacillus adapted to survival in the hostile environment of stomach. It attaches to the surface epithelium beneath the mucous, has high urease activity – produces NH_3 which maintains a neutral microenvironment around the bacteria and promotes back diffusion of H^+ ions. It has been found as a commensal in 20-70% normal individuals, and is now accepted as an important contributor to the causation of chronic gastritis, dyspepsia, peptic ulcer, gastric lymphoma and gastric carcinoma. *H. pylori* generally persists for the life of the host. Up to 90% patients of duodenal and gastric ulcer have tested positive for *H. pylori*.

Two Australian scientists Barry J. Marshall and Robin Warren have won the 2005 Nobel Prize in medicine for the discovery of bacteria which mainly caused gastritis and peptic ulcer i.e. *Helicobacter pylori*.

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Chapter - 2

Drugs acting on Cardiovascular System

DRUGS ACTING ON CARDIOVASCULAR SYSTEM (CVS)

BASIC ASPECTS OF CARDIAC FUNCTION:

The heart, blood, lungs and blood vessels compose an integrated physiological system that supplies oxygen and other nutrients to tissues and removes CO_2 and other waste products. Efficiency of the heart muscle and of tissue functions throughout the body is critically dependent on adequate supplies of oxygenated blood. This necessitates a series of sensitive and dynamic control mechanisms to ensure that cardiac output is sufficient to supply cellular demands.

The three primary pathways by which the heart can increase its cardiac output in response to body needs for increased blood flow are –

(i) An intrinsic response of the muscle to changes in muscle length (Intrinsic Regulation);
(ii) Changes in heart rate (Regulation by Nervous System); and
(iii) Adjustments in contractility (Cellular Regulation).

These physiological control systems are of considerable importance to pharmacology because the net response of the heart to drugs is controlled by these mechanisms.

Intrinsic Regulation:

Contractile response of cardiac muscle to a change in its own length is the primary mechanism whereby the heart adjusts its pumping activity under normal physiological conditions. In the whole heart, the volume of blood returning to cardiac chambers from the veins controls resting muscle length. The fundamental capability of the heart to auto-regulate its pumping capacity in response to end diastolic filling, and thus, muscle length, is referred to as the Frank-Starling law of the heart.

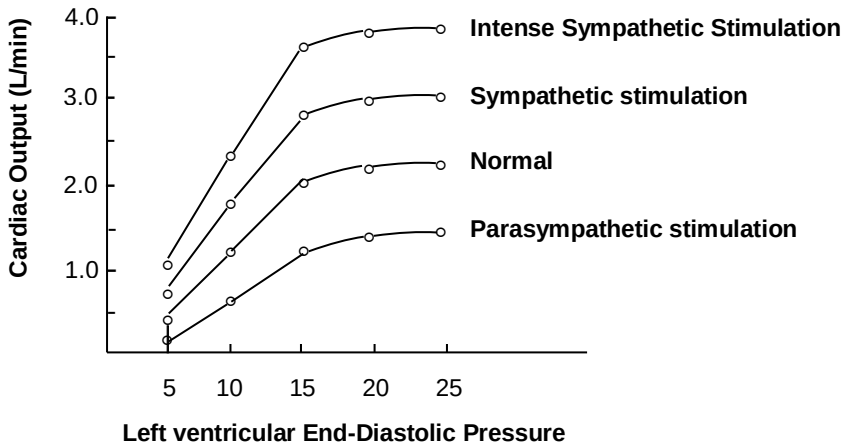

Fig.: Frank-Starling law of the heart. As end-diastolic ventricular pressure increases, the myofibre is stretched, enhancing the contractile state of the muscle; cardiac output is thus increased. The cardiac output curve can be influenced by different degrees of sympathetic and parasympathetic stimulation.

Regulation by the Nervous System**:**

The autonomic nervous system regulates the heart mainly by adjusting cardiac rate and myocardial contractility. Sympathetic stimulation of cardiac muscle markedly increases the force of contraction irrespective of end diastolic muscle length. A change in contractile strength that is independent of muscle length is referred to as a change in contractility (inotropy). In the presence of inotropic stimulation by the sympathetic system, cardiac output at each level of ventricular filling is enhanced considerably over the basal state. Conversely, parasympathetic nerves exert their primary influences on cardiac output, not by changing the inotropic state, but by adjusting heart rate. Vagal discharge produces bradycardia; with fewer heart beats per unit of time, less blood can be pumped and cardiac output is decreased at all levels of venous return.

Cellular Regulation**:**

The basic contractile unit of a heart muscle cell is the sarcomere, composed of actin and myosin. Activation of the filaments is regulated by a protein assembly unit composed of tropomyosin and troponin and associated with actin molecules. Availability of ionized Ca^{2+} in the vicinity of troponin is the obligate modulator of the relaxation-contraction cycle.

HEART FAILURE:

When the heart is no longer able to eject the volume of blood which enters its ventricles, it is in failure and increases in size. Failure, accompanied by increasing oedema or ascites, is commonly a result of myocardial or valvular damage. When it is not possible to correct the failure by dealing with its primary cause, treatment of heart failure follows one or two main approaches –

1. The first is to attempt to increase or improve the pumping ability of the heart (by using cardiac stimulants & cardiac glycosides).
2. The amount of work required of the heart is reduced to a level at which the heart is reduced to a level at which the heart can cope (by using vasodilators).

CARDIAC GLYCOSIDES

These are the glycosides naturally obtained from certain plants and contain active principles which act specifically on the failing heart and make them normal. That is why, they are called cardiac glycosides. Since cardiac glycosides have cardiotonic properties, they are also known as Cardiotonic Drugs. They increase myocardial contractility and output in a hypodynamic heart without a proportionate increase in O_2 consumption. Thus, efficiency of failing heart is increased.

Cardiac glycosides differ from cardiac stimulants in following ways:-

Cardiac Glycosides	Cardiac Stimulants
1. They have only inotropic effect but no chronotropic effect.	(i) Have both inotropic as well as chronotropic effects.
2. Myocardial efficiency is increased because total myocardial O_2 consumption remains unaffected.	(ii) Myocardial efficiency is decreased as the total myocardial O_2 consumption is increased disproportionately.
3. Used in congestive heart failure.	(iii) Used in heart blocks.

SOURCES OF CARDIAC GLYCOSIDES:

Most of the cardiac glycosides are derived from plants.

Source	Glycosides
1. *Digitalis purpurea* (Leaf) {Common foxglove}	Digitoxin, Gitoxin and Gitalin.
2. *Digitalis lanata* (Leaf) {Woolly foxglove}	Lanatosides A → Digitoxin B → Gitoxin, and C → Digoxin
3. *Strophanthus gratus* (Seed)	Ouabain (Strophanthin G)
4. *Strophanthus kombe* (Seed)	Strophanthin K

* Digitoxin and digoxin are used clinically.

By convention, “digitalis” is applied as a collective term for the whole group of glycosides and has come to mean ‘a cardiac glycoside’.

CHEMISTRY OF CARDIAC GLYCOSIDES:

The molecule of a glycoside contains a sugar moiety and a second portion called an aglycone or genin. The aglycone is a steroid alcohol with an unsaturated lactone ring attached at C-17. The various sugars are linked to aglycone at C-3 position.

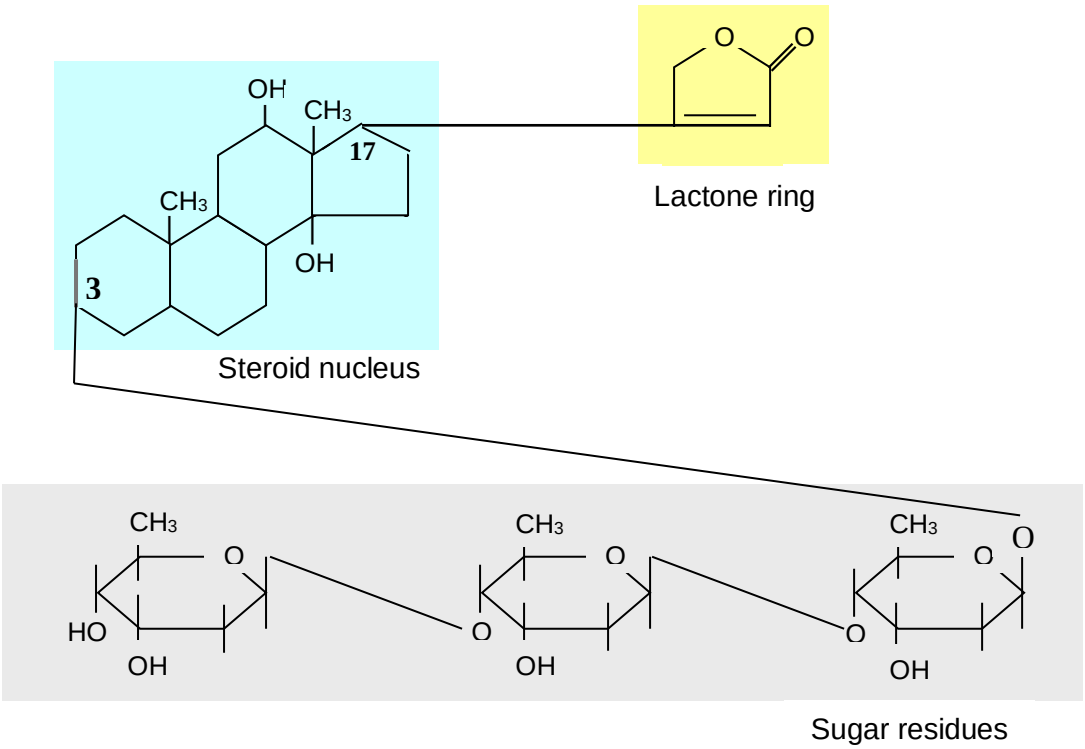

Figure: Structure of digitoxin showing lactone ring, steroid nucleus and sugar residues.

Aglycone (genin): Responsible for the activity of the glycoside. So, the pharmacological actions of cardiac glycosides are due to the aglycone part.

Glycone (Sugar): Responsible for modifying the water and lipid solubility of the glycoside molecule, thus, affecting its potency and duration.

The different aglycone and sugar moieties of cardiac glycosides are shown as below:

Glycoside	Genin	Sugar (s)
Digitoxin	Digitoxigenin	3 molecules of digitoxose
Gitoxin	Gitoxigenin	3 molecules of digitoxose
Gitalin	Gitalligenin	3 molecules of digitoxose
Digoxin	Digoxigenin	3 molecules of digitoxose
Digitalin	Gitoxigenin/ Digitaligenin	1 molecule of digitalose + 1 molecule of glucose
Digitonin	Digitogenin	4 molecules of galactose + 1 molecule of xylose
Gitonin	Gitogenin	3 molecules of galactose + 1 molecule of pentose
Tigonin	Tigogenin	2 molecules of glucose + 2 molecules of galactose + 2 molecules of rhamnose

CARDIOVASCULAR EFFECTS OF CARDIAC GLYCOSIDES:

The principal therapeutic effect of cardiac glycosides on a failing heart (congestive heart failure) is a direct stimulatory effect on force of ventricular contraction i.e. a strong positive inotropic effect. In addition, they also exert an indirect effect, a vagally mediated slowing of heart rate. As a result, sequences of events associated in the genesis of congestive heart failure are reversed as shown below:

Increase in force of contraction
Decrease in heart rate
Increase in cardiac output
Decrease in blood volume
Reduction in venous congestion (pooling)
Increase in renal blood flow
Diuresis and relief of oedema
Return of heart size to normal

} All these effects can be explained on the basis of positive inotropic effect of cardiac glycosides.

MECHANISM OF ACTION OF CARDIAC GLYCOSIDES:

The cardiac glycosides inhibit the Na^+- K^+ - ATPase system located on the surface of myocardial cell membrane and thus interfere with Na^+/ Ca^{2+} exchange resulting in intracellular accumulation of Ca^{2+}. Therefore, more of Ca^{2+} ions are made available to interact with contractile proteins causing increase in force of contraction of myocardium as a whole. The Na^{2+}- K^+ - ATPase is the pharmacological receptor of cardiac glycosides.

CLINICAL USES OF CARDIAC GLYCOSIDES:

1. In the treatment of congestive heart failure (due to strong positive inotropic effect).
2. Atrial fibrillation or flutter – The negative chronotropic effect is exploited in atrial fibrillation when a slowed rate of impulse conduction through the AV node allows the ventricular rate to fall below the atrial and so restores more efficient pumping.

The commonly used glycosides are – Digitoxin, Digoxin and Ouabain. Ouabain is the most potent (acts very rapidly and its effects disappear soon) and therefore used in emergency therapy. However, it is ineffective orally. In ruminants, parenteral digitalization is recommended as the glycosides are ineffective after oral dosing (inactivation in rumen & reticulum).

DIGITALIZATION:

It is the procedure followed for administration of cardiac glycosides. It consists of initial administration of large dose (in 3-5 divided doses) on first one to two days to obtain an observable response (digitalization dose). Once the effect is noticed, the animals are treated with daily doses to sustain the desired effect (maintenance dose). The quantity of drug necessary to achieve the initial response is commonly designated the digitalization dose or loading dose, whereas the daily dose needed to maintain this level of therapeutic action is called the maintenance dose. The loading dose is about 2-5 times the maintenance dose.

Generally three types of digitalization are practiced:-

1. **Intensive digitalization:** In this method, half of the calculated dose is given immediately, followed by a quarter of the dose 6 hour later and $1/8^{th}$ every 4-6 hour thereafter until signs of toxicity occur (vomiting, diarrhea, depression and cardiac irregularities).
2. **Rapid digitalization:** It consists of giving the calculated digitalization dose in thirds at intervals of 6 hour followed by the maintenance dose thereafter, adjusted if necessary to the needs of the individual.
3. **Slow digitalization:** It consists of administration of $1/5^{th}$ of the total dose at 10 hour intervals during the first two days in mild cases. This is the safest of the dosing regimens and is generally preferred for non-hospitalized patients.

ANTIARRHYTHMIC DRUGS

These are the drugs used to prevent or treat irregularities of cardiac rhythm. An arrhythmia is an abnormality in the rate, regularity, or site of origin of cardiac impulse or a disruption in impulse conduction such that the normal sequence of atrial and ventricular activation is changed. It is often associated with imbalance of the parasympathetic and sympathetic branches of the autonomic nervous system; changes in serum electrolyte concentrations esp. K^+ and Ca^{2+} ions; hypoxemia; acidosis; changes in concentration of CO_2; excessive stretch of cardiac tissue; mechanical trauma; myocardial disease states such as congestive heart failure and viral myocarditis; numerous drugs; ischaemia and infarction of heart muscle.

Drugs which control arrhythmia (antiarrhythmic drugs) either raise the threshold for excitation or prolong the refractory period of the pacemaker or ectopic pacemakers and so may influence automaticity, speed of conduction, excitability and myocardial contractility.

CLASSIFICATION OF ANTIARRHYTHMIC DRUGS:

On the basis of mechanism of action, Vaughn Williams (1984) classified antiarrhythmic drugs into four classes (Class I to IV).

1. Class – I Drugs (Local anaesthetic agents or membrane stabilizers):

- Potent local anaesthetic for nerves, as well as the myocardial cell membrane, but this activity is generally more pronounced in the heart than in nerve fibres.
- Reduces maximal rate of depolarization (phase 0) of cardiac fibres.
- Also, there is increase in threshold of excitability; decrease in conduction velocity; and prolongation of refractory period.
- Class – I drugs can control arrhythmias caused by enhanced automaticity.
- 'Quinidine' is the original and prototype class –I drug, so the group is also referred to as "Quinidine – like antiarrhythmic drugs".

Some important dissimilarities exist, however, relative to the precise effects of different class – I drugs on phase 0 depolarization in normal and abnormal cells, action potential duration and length of refractoriness, Keefe *et al.* classified class – I agents into 3 subdivisions:-

(i) Subclass IA **:** (Quinidine, Procainamide and Disopyramide)

- Consistent reduction of the rate of phase 0 depolarization in normal and injured cardiac cells.
- Uniformly prolong the cardiac action potential & refractory period.

Quinidine: It is the dextroisomer of quinine (alkaloid of *Cinchona* bark). Quinine is an antimalarial compound. It has also some antiarrhythmic activity. Quinidine is more effective than quinine as an antiarrhythmic drug. So, Quinidine is a drug of choice for controlling atrial fibrillation.

Procainamide: It is an amide derivative of a local anaesthetic procaine. It is less rapidly inactivated as compared to procaine.

(ii) Subclass IB : (Lidocaine, Phenytoin, Tocainamide, Mexiletine and Aprindine)

* Reduction of phase 0 depolarization and conduction velocity in injured cardiac cells but this feature is much less in normal cardiac cells.

Lidocaine: This is the only clinically used local anaesthetic in the group of myocardial depressants, all of which however, possess local anaesthetic activity. It should not be administered orally because a maximum percentage of the drug is metabolized in liver before reaching into the circulation.

Phenytoin: This antiepileptic drug has now been used extensively in man to control digitalis – induced and ventricular dysrhythmias.

(iii) Subclass IC : (Encainide, Lorcainide and Flecainide)

* Markedly depress the maximal rate of phase 0 depolarization in normal and abnormal cardiac cells.
* There is little effect on refractoriness and action potential.

2. Class – II Drugs (Antiadrenergic drugs):

- Clinically useful class – II drugs are β blocking agents.
- Propranolol is the prototype of class – II. Other drugs in the class are Oxyprenolol, Alprenolol, Metoprolol, Timolol and Pindolol.
- The basis of classifying agents that block cardiac sympathetic stimulation into a separate category derives from the fact that hyperactivity of the sympathetic nervous system is an important factor in pathogenesis of different types of arrhythmias, esp. tachyarrhythmias associated with ectopic pacemaker foci.

Propranolol: It is a non-selective β adrenoceptor blocker having three important indications – cardiac arrhythmia, angina pectoris and hypertension.

3. Class – III Drugs (Agents widening action potential):

- Produce 'pure' prolongation of action potential, thereby extending the refractory period.
- e.g. Amiodarone (an antianginal drug), Bretylium (adrenergic neurone blocker).

Bretylium: Basically, it is a NE release blocker. But, the drug has also direct effects on heart.

4. Class – IV Drugs (Ca^{2+} Antagonists/ Ca^{2+} Channel Blockers):

- Little effect on fast Na^{+} channels but have relatively specific inhibitory effects on Ca^{2+} dependent slow responses.
- Ca^{2+} current participates in AV nodal conduction. So, Ca^{2+} blockers slow AV conduction and thereby have application for controlling supraventricular arrhythmias that involve AV reentry pathways.
- e.g. Verapamil (prototype drug).

Verapamil: At first, in man, it was introduced as a coronary vasodilator. Later, it was used to control dysrhythmias of atrial origin.

CLINICAL USES OF ANTIARRHYTHMIC DRUGS:

In cases of atrial fibrillation, ventricular tachycardia, sinus tachycardia, ventricular premature complexes.

VASODILATORS and ANTIHYPERTENSIVE DRUGS

Drugs which cause blood pressure to fall are known as Hypotensive or Antihypertensive drugs. Vasodilators are drugs which cause dilatation of blood vessels and decrease blood pressure.

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS:

1. **Diuretics:** (a) Thiazide and related agents. e.g. Hydrochlorothiazide.
   (b) High ceiling diuretics. e.g. Furosemide.

   Diuretics enhance Na^+ excretion and thereby speed up the resorption of oedema fluids, reduce blood volume and prevent refractoriness. These drugs do not lower the blood pressure in normotensives.

2. **Sympatholytic drugs:**
   (a) Centrally acting agents. e.g. Methyldopa, Clonidine etc.
   (b) Ganglionic blocking agents. e.g. Trimethaphan.
   (c) Adrenergic neuron blocking agents. e.g. Reserpine.
   (d) β Adrenergic antagonists. e.g. Propranolol, Metoprolol, Atenolol etc.
   (e) α Adrenergic agents. e.g. Prazosin, Phenoxybenzamine, Phentolamine etc.
   (f) Mixed antagonists. e.g. Labetolol (both α & β blocker).

3. **Calcium channel blockers:**

   Among the more modern arteriolar vasodilators, these drugs are able to inhibit vascular smooth muscle tone by blocking calcium entry via voltage dependent channels and, in higher concentration, to inhibit the release of calcium ions from sarcoplasmic reticulum. Both mechanisms reduce the availability of Ca^{2+} to the contractile apparatus of myocardial and smooth muscle cells.

   e.g. Verapamil, Nifedipine, Diltiazem etc.

4. **Directly acting vasodilators:**
   Arteriolar vasodilators: Hydralazine, Minoxydil, Diazoxide etc.
   Arteriolar + *Venous*: Sodium nitroprusside.

5. **Indirectly acting vasodilators (Inhibitors of Angiotensin Converting Enzyme):** These are the most appropriate antihypertensives in patients with diabetes, nephropathy, left ventricular hypertrophy, congestive heart failure and angina. These drugs inhibit conversion of inactive angiotensin I to angiotensin II and/ or angiotensin III, which is mediated by an angiotensin converting enzyme (ACE, a kinase - II) and thus prevent constriction of arteriolar smooth muscles and rise in blood pressure. e.g. Captopril, Enalpril, Lisinopril etc.

The vasodilators have immense therapeutic value in man as antihypertensives and in the treatment of angina pectoris. In veterinary practice, they are of limited value and occasionally used in cases of congestive heart failure, in combination with digitalis to reduce the load on the failing heart (by causing peripheral vasodilatation).

VASOCONSTRICTORS

Vasoconstrictors elevate blood pressure by a peripheral mechanism i.e. they reduce the volume of the circulatory space and so increase peripheral resistance and ventricular after-load. These drugs were formerly used in circulatory collapse but alternative forms of treatment are now preferred.

The use of sympathomimetic vasoconstrictors are now restricted to the local control of small vessel haemorrhage, the shrinkage of swollen mucous membranes and the treatment of acute vasodilatation. Blood pressure can be elevated by adjustment of the circulating volume of blood, by use of medullary stimulants or by the use of non-sympathomimetic vasoconstrictors (e.g. angiotensin).

HAEMATINICS (Antianaemic Drugs)

These are agents required in the formation of blood, and are used for the treatment of anaemias. Anaemia occurs when the balance between production and destruction of RBCs is disturbed either by blood loss (acute or chronic) or impaired red cell formation due to deficiency of essential factors i.e. Fe, Vitamin B_{12}, folic acid etc. and/or bone marrow depression (hypoplastic anaemia), erythropoietin deficiency.

Some Important facts about blood and blood elements:

- Blood volume is typically about 8% of body weight; approximately 40% of this consists of cellular elements (erythrocytes, leucocytes and thrombocytes) and about 60% consists of plasma.
- More than 99% of blood cells are erythrocytes, and their principal function is to transport haemoglobin (Hb), which in turn carries oxygen from the lungs to the tissues and CO_2 from tissues to the lungs, etc.
- The blood of domestic animals carries between 15 and 20 ml of O_2 per 100 ml of arterial blood.
- 1 gm of Hb combines with approximately 1.36 ml of oxygen.
- The principal site of erythropoiesis in healthy, adult animals is the bone marrow, whereas “extramedullary haematopoiesis” may also occur in the spleen and liver *in utero*, in neonates and in domestic adults when the bone marrow regenerative response is inadequate.
- Insufficient tissue oxygenation is a major determinant of the rate of erythropoiesis. Renal hypoxia provides for the synthesis of erythropoietin (synthesized by kidney), a protein which accelerates erythropoiesis in bone marrow.
- Anaemia due to deficiency of Fe, Cu, Co or dietary protein – Microcytic hypochromic anaemia. [NB – Piglet anaemia due to deficiency of iron (a nutritional anaemia) is also microcytic hypochromic].
- Anaemia due to deficiency of Vitamin B_{12} and folic acid – Macrocytic hyperchromic anaemia.

Mucosal Block:

Body does not excrete iron. So, the gut has a mechanism to prevent reentry of excess iron in the body. Iron reaching inside mucosal cell is either transported to plasma or oxidized to ferric form and complexed with apoferritin to form ferritin. This ferritin generally remains stored in the mucosal cells and is lost when they are shed (life span 2-4 days). This is called the "Ferritin Curtain".

The iron status of the body and erythropoietic activity govern the balance between these two processes, probably through a 'haematopoietic transcription factor', and thus the amount of iron that will enter the body: a larger percentage is absorbed during iron deficiency. When body iron is low or erythropoiesis is occurring briskly, ferritin is either not formed or dissociates soon and released iron is transported to the blood.

Based on the observation that when body does not require iron, only a small amount of this element that enters into the mucosal cell is moved in plasma. So, the major barrier to the absorption of excess iron is the mucosal cell. This is called mucosal block.

Mucosal block however, can be overwhelmed by gross excess of Fe.

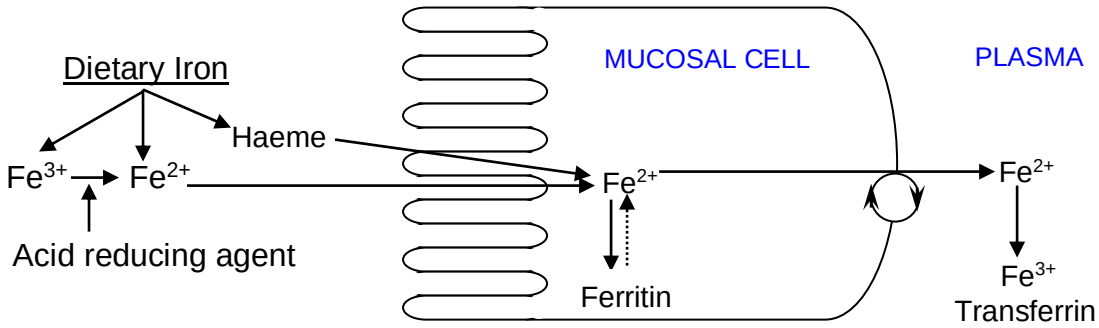

Fig.: Schematic representation of intestinal absorption of iron and the mucosal block

Antianaemic drugs can be classified according to their etiology as follow:

[I]. AGENTS USED IN IRON DEFICIENCY ANAEMIAS: Iron is essential for formation of haemoglobin.

(A) Iron compounds:

(1) Ferrous sulphate: Daily oral doses are as follows:

Dog – 100 to 300 mg/kg per day

Cat – 50 to 100 mg/kg per day

Cattle – 8 to 15 gm/kg per day for 2 weeks or more

Horse – 2 to 8 gm/kg per day for 2 weeks or more

Swine, sheep & goat – 0.5 to 2 gm/kg per day for 2 weeks or more.

(2) Ferrous gluconate/ ferrous succinate/ ferrous lactate/ ferrous fumarate/ ferrous ammonium citrate:

In small animals – 0.25 gm/kg per day for 2-3 days orally.

(3) Iron dextran preparations (Parenteral): [Imferon®]

Piglets – 2 ml containing 100 mg of ferric iron i.m. on 2nd or 3rd day of birth, repeat after 10 days if necessary.

Dog – 10 to 20 mg/kg i.m.

Neonatal cat – Single injection of 50 mg i.m. at 18th day of age to prevent congenital iron deficiency anaemia.

(B) Copper compounds: They are essential for utilization of iron, which include copper sulphate (sow - 80 mg, cow - 200 mg i.v.) and copper glycinate (sow - 45 mg, cow - 120 mg i.m.).

[NB: A combination of $FeSO_4$ and $CuSO_4$ (5:1) is used for the treatment of piglet anaemia.**]**

[II]. AGENTS USED IN COBALT DEFICIENCY ANAEMIAS:

Cobalt is utilized by ruminal microflora for the synthesis of Vitamin B_{12}. Cobalt deficiency in ruminants is associated with a marked anaemia, loss of appetite, progressive wasting, decrease in blood volume and a drop of oxygen carrying capacity to 30% of normal, or lower in sheep. The condition is widely known as Pine (UK), Bush sickness (New Zealand), Nakuritis (Kenya) or Grand Traverse Disease (USA).

Cobalt chloride or cobalt sulphate:

For prophylaxis	For treatment	
Cattle – 25 mg/day *per os*	Cattle – 0.5 gm	through feed or drench
Calves – 10 mg/day *per os*	Calves – 0.2 gm	
Sheep – 5 mg/day *per os*	Sheep – 0.1 gm	
Lamb – 2.5 mg/day *per os*	Lamb – 0.05 gm	

[III]. AGENTS USED IN VITAMIN DEFICIENCY ANAEMIAS:

Deficiency of vitamin B_{12} and folic acid, which are B-group vitamins, result in megaloblastic anaemia characterized by the presence of large red cell precursors in bone marrow and their large and short-lived progeny in peripheral blood. They are, therefore, called maturation factors. The basic defect is in DNA synthesis. Apart from haematopoietic, other rapidly proliferating tissues also suffer.

Folic acid and vitamin B_{12} act sequentially in the pathway which leads to the synthesis of nucleoproteins in cell division.

In addition to the above two vitamins, riboflavin and pyridoxine may also act as haematinic vitamins.

BLOOD COAGULANTS (HAEMOSTATICS)

These are the agents which promote coagulation, and are indicated in haemorrhagic states. These are used locally as well as systemically; and accordingly they are classified as given below:

LOCAL (TOPICAL) COAGULANTS:

[A] Natural or Physiological Coagulants:

1. **Thromboplastin:** It is produced naturally by platelets and tissues in response to trauma. The commercial preparation is a powder extracted from bovine brains or from acetone extracted lung and/or brain of rabbits. It aids haemostasis by promoting conversion of prothrombin to thrombin, thereby accelerating the coagulation process. It is employed as a local haemostatic in surgery when applied by spray or direct application in a sponge.
2. **Thrombin:** It is a white sterile powder prepared by interaction of Thromboplastin and calcium with prothrombin of bovine origin. In control of bleeding, thrombin converts endogenous fibrinogen to fibrin for clot formation. It is useful where there is bleeding from parenchymatous tissue, cancellous bone, dental sockets, laryngeal and nasal surgery and reconstructive surgery.
3. **Fibrinogen:** It is concentrated fraction of normal human plasma and is available as sterile white powder. It is principally used on denuded mucous membranes and as an adhesive in skin grafts (2% solution).
4. **Fibrin foam:** It is a sponge like material prepared by action of thrombin on human fibrinogen. It is an insoluble substance marketed as strips of fine white sponge. It may be applied directly, with pressure, to the haemorrhagic area or after presoaking it in thrombin solution. This preparation acts as a preformed network to trap blood oozing from the surface area.

[B] Synthetic or Surgical Coagulants:

These are used to prevent bleeding during surgery.

1. **Absorbable gelatin sponge:** It is a sterile, water-insoluble, gelatin base sponge. It is non-antigenic and will absorb several times its weight of whole blood. This denatured gelatin usually is soaked in bovine thrombin and left in the bleeding area following closure of operative wounds. When applied to the surface of the body or mucosal membranes, it liquefies within 3-5 days. Gelatin sponge is completely absorbed in 4-6 weeks. It is used primarily for capillary or venous bleeding.
2. **Oxidized Cellulose:** It is a surgical gauge containing oxidized cellulose. When kept over the bleeding surfaces, it helps in formation of clot. It should be used only as temporary packing because its permanent implantation in tissues and fractures interferes with bone regeneration and may result in cyst formation. It is available as sterile cotton pledgets (pads) and gauge pads and strips.

SYSTEMIC COAGULANTS:

These are drugs which promote blood coagulation and used systemically in the treatment of haemorrhagic syndromes. These are –

1. **Whole blood:** Whole fresh blood or blood components are indicated for emergency treatment of acute haemorrhagic syndromes associated with deficiency of clotting factors or platelets.
2. **Vitamin K:** It is a fat soluble dietary principle required for the synthesis of clotting factors II, VII, IX and X in the liver.

   Vitamin K exists in 3 main forms:-

   Vitamin K_1 (Phytonadione or Phylloquinone) – It is present in plants.

   Vitamin K_2 (Menaquinone) – It is produced by micro-organisms.

   Vitamin K_3 (Menadione) – Synthetic derivative.
3. **Protamine sulphate:** It is a low molecular weight protein found in the sperm of certain fishes. It is strongly basic and combines with acidic heparin to form a stable salt that prevents any further anticoagulant activity of heparin. It is available as a 1-2% solution. It is administered slowly by i.v. route at a rate no greater than 50 mg over a 10 minute period.

ANTICOAGULANTS

These are the agents which prevent clotting of blood. The principal use of anticoagulant agents is *in vitro* to prevent clotting of blood for transfusion or diagnostic use and in vivo to prevent development and enlargement of thrombi.

[A] IN VITRO ANTICOAGULANTS:

Essentially two categories of chemicals are used:-

(i) Those employed as anticoagulants in samples of blood intended for physical or chemical examination (diagnostic purpose).

(ii) Those employed to preserve blood for transfusion (transfusion purpose).

(I) Anticoagulants used in laboratory examination of blood:

2. **Sodium oxalate** (20% concentration) @ 0.01 ml/ml (2 mg/ml) of blood.
3. **Sodium citrate** (25% concentration) @ 0.01 ml/ml (2.5 mg/ml) of blood.
4. **Sodium EDTA** @ 0.1 mg/ml of blood.
5. **Heparin sodium** @ 7.5 units per ml of whole blood.

(II) Anticoagulants used for blood and blood components transfusion: These have preservative effects. These are –

1. **Acid-citrate-dextrose (ACD solution):** It consists of Na citrate – 25 gm, citric acid – 8 gm, dextrose – 24.5 gm given at the level of 15 ml/ 100 ml of blood.

2. **Citrate-phosphate-dextrose-adenine (CPDA-1):** It is now the most commonly used anticoagulant in human and veterinary transfusion medicine. It can maintain a high level of erythrocyte post-transfusion viability up to 20 days in dogs.

[B] <u>IN VIVO ANTICOAGULANTS or Systemic anticoagulants</u>:

These are used systemically to prevent intravascular thrombus formation (pulmonary embolism). These are divided into two groups based on their route of administration as described below:-

(I) Intravenous anticoagulants:

Heparin sodium: In body, it is present in mast cells along with histamine and 5-HT (connective tissue, liver, lungs etc.). It is supposed to act as a natural anticoagulant helping blood to remain in liquid state. It is inactive orally. It is injected i.v. in normal saline or dextrose @ 1 unit per ml.

(II) Oral anticoagulants:

Coumarin derivatives {Warfarin, Phenprocoumon, Acenocoumarol and Indanedione derivatives (Anisindione)} – Their veterinary clinical application is not established. Bishydroxycoumarin is the cause of haemorrhagic syndrome observed in sweet clover (dicoumarol) poisoning in cattle.

MECHANISM OF ACTION OF ANTICOAGULANTS:

Sodium oxalate Sodium citrate Sodium EDTA	}	Prevents participation of Ca^{2+} ions in blood clotting process, by formation of insoluble calcium salts with citrates, oxalates and EDTA. Ca^{2+} ions are necessary for conversion of prothrombin to thrombin and activation of factors IX and X.
Heparin	—	Inhibits thrombin formation and prohibits activation of factors IX, X, XI and XII. Also prevents clumping of platelets.
Coumarins	—	Antagonists of vitamin K and thus prevents activation of factors II, VII, IX and X.

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Chapter - 3

Drugs acting on Respiratory System

DRUGS ACTING ON RESPIRATORY SYSTEM

In addition to the cough and sneeze reflexes, two other systems provide the major defense of the respiratory tract against invading organisms or foreign materials: the mucociliary apparatus and the respiratory mononuclear phagocyte system (MPS).

The mucociliary apparatus is the first major defense and consists of the ciliary lining of the tracheobronchial tree and the fluid blanket surrounding the cilia. Two types of secretions form the fluid blanket of the respiratory tract. The cilia must be surrounded by a low viscosity, watery medium to maintain their rhythmic beat. A more mucoid layer lies on top of the cilia. The synchronous motion of the cilia causes the cephalad movement of the mucous layer and any trapped materials. The normal composition of the combined secretions of the tracheobronchial tree is 95% water, 2% glycoprotein, 1% carbohydrate and less than 1% lipid. Glycoproteins increase the viscosity of the secretions, providing protection and lubrication. Changes in the viscoelastic properties of mucous such that it becomes either too watery or too rigid will result in mucous transport that is less than optimal.

The second major component of the pulmonary defense system is the respiratory MPS. In cats, calves, pigs, sheep, and goats, this includes both alveolar macrophages and pulmonary intravascular macrophages (PIMs). The PIMs are resident cells that are characterized by phagocytic properties and thus cause the release of inflammatory mediators. The pharmacological significance of the MPS reflects its role in inflammation.

At times, these defense mechanisms are broken in pathological states which may result in cough, bronchoconstriction, congestion etc.

The drugs described in this chapter are those used for effects on mechanical and other functional aspects of the respiratory tract and are most commonly used in combinations. Their most frequent use is in the respiratory system when ventilation is impeded, has become distressing or has become so inadequate that abnormal blood gas concentrations are present.

EXPECTORANTS or Mocokinetics

These are the drugs which increase the fluidity and volume of respiratory secretions resulting in productive cough and promote pulmonary drainage during inflammatory conditions of the respiratory tract (pneumonia and bronchitis). These are used as adjuvants for the management of cough because they facilitate removal of the inciting cause.

They have been classified into the following types according to their mechanism of action:-

1. Inhalant Expectorants or Stimulant Expectorants:

These agents promote repair of chronic inflammatory processes in respiratory tract and consist of aromatic compounds, which irritate the respiratory passages causing hyperaemia. These agents either heated or dissolved in steaming water are intended for inhalation in a confined air space. Examples:

- Terebene: It is obtained by distillation of turpentine oil which has been treated with sulphuric acid.

  Dose - Horse & Cattle – 30 to 120 ml
  Sheep & Goat – 4 to12 ml
  Pig – 2 to 8 ml
  Dog – 0.25 to 1 ml.

- Vapours of Tr. Benzoin, Eucalyptus oil, Lemon, Anise and Turpentine oil – These increase respiratory secretions and lessen cough.
- Wood tar derivatives: Guaiacol and its glyceryl ether, guaiphenesin (glycerol guaiacolate). These agents help to increase airway particle clearance.

2. Ingested Expectorants or Reflex or Nauseant Expectorants:

They are all administered by mouth. Some are nauseants i.e. drugs which can induce vomiting, but are administered in subemetic doses. Others are absorbed from the gut and are excreted, at least in part via the bronchial mucosa. These agents increase respiratory secretions due to their nauseant effect and thereby loosen a dry harsh cough. Examples –

- Ipecacuanha (Ipecac): Emetic expectorant action is due to an alkaloid emetine.

  Dose of Tr. Ipecacuanha - Horse – 8 to 30 ml
  Dog – 0.5 to 4 ml
  Cat – 0.5 to 1 ml

  In addition to ipecac; Squill, Balsam of Tolu and Cocillana may also be used.

- Antimony potassium tartarate (Tartar emetic):

  Dose - Large Animals – 2 to 4 gm
  Sheep, Goat & Pig – 0.1 to 0.5 gm
  Dog – 2 to 3 mg.

3. Saline Expectorants:

These reflexly increase mucous secretion after oral administration. Examples-

- Ammonium Chloride – Large Animals – 8 to 16 gm
  Small animals – 250 to 500 mg.
- Potassium Iodide and Sodium Iodide.

These are all excreted in bronchial secretions after oral administration and cause expectorant action.

4. Demulcent Expectorants:

These have smoothening effect on respiratory tract mucosa and thus reduce its irritation. Example – Syrup.

5. Mucolytic Expectorants:

These make bronchial secretions easier to propel by ciliary action or to expel by coughing and in this way reduce cough frequency. They can be regarded as expectorants, although their major action is not that of increasing the volume of secretions or diluting too viscous secretions. Examples:-

- Sodium acetylcysteine solution 20%: It is inhaled in the form of spray or aerosol. It is believed that the sulphydryl group of acetylcysteine breaks disulphide bonds in the glycoproteins in exudates and so, changes the physical property of the exudates. 2 or 3 times exposure with positive pressure is helpful.
- Bromhexine: A derivative of the alkaloid vasicine obtained from *Adhatoda vasica* (Vasaka), is a potent Mucolytic capable of inducing thin copious bronchial secretion. It depolymerises mucopolysachharides directly as well as by liberating lysosomal enzymes – network of fibres in tenacious sputum is broken.

  Dose – Small animals – 1 mg/kg bid orally for 7 days.

  Horse – 0.1 to 0.25 mg/kg bid orally for 7 days.
- Dembrexine: It is a more recent entrant into the equine market.

ANTITUSSIVES
(Cough Sedatives or Cough Suppressants)

These are the agents which suppress cough. The goal of antitussive therapy is to decrease the frequency and severity of cough without impairing mucociliary defenses. Cough suppressants should be used cautiously and are contraindicated if cough is productive.

[I] CENTRALLY ACTING ANTITUSSIVES:

Centrally acting antitussives are classified as narcotic and non-narcotic drugs.

(1) Narcotic Antitussives:

Narcotic antitussives depress the cough centre sensitivity to afferent stimuli. However, they can be associated with strong sedative properties, as well as constipation when administered chronically. Codeine and hydrocodone are the narcotics most commonly used to control coughing. They can be used for cough suppression in both dogs and cats.

(i) Codeine (Methylmorphine)**:**

It is one of the most effective drugs available to suppress the cough reflex. Codeine phosphate or codeine sulphate can be used. Compared to morphine, codeine is equally effective as a cough suppressant but is less suppressing to other central centres and causes less constipation.

(ii) Hydrocodone**:**

It is a more potent antitussive than codeine but causes less respiratory depression. It is probably the most commonly used antitussive in dogs. Hydrocodone bitartrate is a hydrolysis product of dihydrothebaine.

(2) Non-narcotic Antitussives:

Non-narcotic antitussives commonly used in veterinary medicine include the narcotic agonist-antagonist butorphanol and dextromethorphan. These agents do not share addictive properties.

(i) Butorphanol**:**

As an antitussive, it is 100 times more potent than codeine. Butorphanol tartrate is a potent antitussive when given orally or parenterally in dogs and cats.

(ii) Dextromethorphan**:**

It is a semi-synthetic derivative of opium which lacks its narcotic properties. Sedation is unusual following its use. Only the l - isomer has antitussive activity, which is similar to codeine in potency. It is generally used in small animals, safely in cats.

(Dextromethorphan + Bronchodilator) is a superior combination as compared to dextromethorphan alone.

(iii) Noscapine**:**

It is a non-addictive opium alkaloid which has antitussive effects similar to codeine. Its use in small animals appears to be limited.

[II] PERIPHERALLY ACTING ANTITUSSIVES:

Bronchodilators are powerful peripheral antitussives, because they relieve irritant-receptor stimulation induced by mechanical deformation of the bronchial wall during bronchoconstriction. e.g. Ephedrine.

Other peripheral antitussives include demulcents like honey, mucokinetic agents and hydrating agents.

BRONCHODILATORS

These are the drugs which relax the smooth muscles of bronchi and cause dilatation of respiratory passages. They are aimed to relieve respiratory distress that is observed during asthmatic attacks. Acute asthma or severe bronchoconstriction may be due to hyper-parasympathomimetic activity or liberation of excess histamine in the bronchi. Other autacoids like 5-HT, prostaglandins and leucotrienes are also involved in the genesis of bronchoconstriction. The condition may be relieved by administering bronchodilators.

Because of a shared mechanism of action, most drugs that induce bronchodilation also reduce inflammation.

Rapidly acting bronchodilators include – β receptor agonists, methylxanthines, cholinergic antagonists and mast cell stabilizers.

1. β receptor agonists:

β receptor agonists are the most effective bronchodilators because they act as functional antagonists of airway constriction, regardless of the stimulus. e.g. Ephedrine.

2. **Methylxanthine derivatives:** Examples – Theophylline and Aminophylline.

   As with β agonists, theophylline is equally effective in large and small airways. In addition to its bronchodilator effects, it inhibits mast cell degranulation and thus mediator release, increases mucociliary clearance, and prevents microvascular leakage. A major advantage of theophylline compared to other bronchodilators is increased strength of respiratory muscles and thus a decrease in the work associated with breathing. This may be important to animals with chronic bronchopulmonary disease.

3. **Anticholinergics:**

   Examples – Ipratropium bromide (A synthetic derivative of atropine). Ipratropium bromide is pharmacologically superior to atropine. It causes greatest bronchodilation (twice as much as atropine) with least side effects (salivation, alteration of mucociliary transport etc.)

4. **Mast cell stabilizers:** Example - Cromoglycate

   Cromoglycate sodium inhibits Ca^{2+} influx into mast cells, thus, preventing mast cell degranulation and the release of histamine and other inflammatory mediators. Thus, it helps in relieving bronchial diseases.

RESPIRATORY STIMULANTS

These drugs help in stimulation of depressed respiration that is associated with excess dosage of anaesthetics. Based on mode of action, they are classified into two groups –

1. **Local or reflex stimulants:** Inhalation of ammonia gas from a strong solution of ammonia or ammonium chloride reflexly stimulates both respiratory and vasomotor centres.
2. **Analeptics:** These drugs stimulate respirations by a direct action on the respiratory centre. They also stimulate the vasomotor centre. Examples –
   (i) Doxapram – It directly stimulates chemoreceptors of the carotid and aortic regions. It also stimulates the medullary respiratory centre. Doxapram is considered superior to all combinations of analeptic agents.
   (ii) Nikethamide – It is less effective as compared to doxapram. The respiratory stimulants are of value in reviving the sinking animals as long as the heart continues to beat.

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Chapter – 4

Drugs acting on Urogenital System

DRUGS ACTING ON UROGENITAL SYSTEM

DIURETICS

These are substances which increase the quantity of urine and electrolyte excreted in a given period. Most diuretic drugs increase urine volume by reducing the efficiency of sodium resorbing processes, and so increase obligatory water loss. These drugs are used to increase urine flow when there is fluid retention and oedema or ascites, e.g. in heart failure, liver disease, hypoproteinaemia, inflammation or trauma, to induce urine flow in renal failure, to create the forced extraction of poisons or drugs in overdose, and to reduce blood pressure. The diuretics in many instances provide symptomatic relief only and attention to the primary cause of the oedema (e.g. in pulmonary oedema) is essential.

CLASSIFICATION OF DIURETICS:

1. High Efficacy Diuretics (Inhibitors of Na^+-K^+-$2Cl^-$ symport):
   (a) Sulphamoyl derivatives – Furosemide, Bumetanide
   (b) Phenoxyacetic acid derivatives – Ethacrynic acid.
   (c) Organomercurials – Mersaryl.
2. Medium Efficacy Diuretics (Inhibitors of Na^+-Cl^- symport):
   (a) Benzothiazides (Thiazides) – Chlorothiazide, Hydrochlorothiazide, Benzthiazide, Hydroflumethiazide, Clopamide.
   (b) Thiazide like (related heterocyclics) – Chlorthalidone, Metolazone, Xipamide, Indapamide.
3. Weak or Adjunctive Diuretics:
   (a) Inhibitors of Carbonic Anhydrase – Acetazolamide
   (b) Aldosterone Antagonists – Spironolactone
   (c) Potassium Sparing Diuretics (Inhibitors of renal epithelial Na^+ channel) – Triamterene, Amiloride.
   (d) Osmotic Diuretics – Mannitol, Isosorbide, Glycerol.
   (e) Xanthines – Theophylline.

(1) High Ceiling Diuretics or Loop Diuretics (Inhibitors of Na^+-K^+-$2Cl^-$ symport):

Drugs belonging to this class are among the most potent and most commonly prescribed diuretics, and all share a common mechanism of action. By blocking a key sodium transport mechanism in the thick ascending limb of loop of Henle (hence the name loop diuretics), the drugs inhibit reabsorption of approximately 25% of the filtered sodium load. Nephron segments distal to the thick ascending limb are incapable of reabsorbing the additional solute, leading to a marked (or high ceiling) natriuresis and diuresis. Furosemide (Lasix®) is the most commonly used diuretic in veterinary medicine. Other drugs in this class include ethacrynic acid, bumetanide and a recent addition torsemide.

Uses: Treatment of oedema of cardiac, hepatic or renal origin.
Dose of Furosemide –
Dog – 2 to 5 mg/kg every 4-6 hours i.v., i.m. or s.c.
(1 to 3 mg/kg every 8-24 hours *per os* for chronic use)
Cat – 1 to 2 mg/kg every 12 hours i.v., i.m. s.c. or oral.

(2) Thiazide and related diuretics (Inhibitors of Na^+-Cl^- symport):

The primary site of action of these diuretics is the cortical diluting segment or the early distal tubule. Here, they inhibit Na^+-Cl^- symport at the luminal membrane. Therefore, sodium and chloride are excreted accompanied by large volumes of water. e.g. Chlorothiazide, Hydrochlorothiazide etc.
Uses: Treatment of oedema of cardiac, hepatic or renal origin. Also hypertension.

(3) Carbonic Anhydrase Inhibitors:

Acetazolamide – Oral & parenteral
Dichlorphenamide, Methazolamide – Oral
Dorzolamide – Topical use.

These drugs are reversible inhibitors of carbonic Anhydrase (in the tubular epithelial cells in proximal tubule) which catalyses the reaction $CO_2 + H_2O \leftrightarrow H_2CO_3$. The carbonic acid is then split into H^+ ions and HCO_3^- ions. When the enzyme is inhibited, H^+ ions will not be available for exchange with sodium ions. Therefore, sodium remains in the tubular lumen which is excreted along with large volumes of water.
Uses: Management of glaucoma.

(4) Aldosterone antagonists: Spironolactone.

These drugs act by diminishing the operation of the Na^+ active resorption system normally activated by the endogenous steroid hormone aldosterone in the distal tubule. Although, only the last few percent of filtered sodium is subject to its control, aldosterone is still vitally important to sodium conservation. The most potent antagonist, spironolactone is a steroid lactone which acts by competing with aldosterone for the site on its receptor protein in renal tubule cells with consequent loss of sodium conserving gene product.
[Canrenone is the active metabolite of spironolactone].
Uses: Hepatic cirrhosis

(5) Potassium sparing diuretics (Inhibitors of renal epithelial Na^+ channel):

Triamterene and Amiloride.

These cause a mild increase in excretion of NaCl and a retention of K^+. Both drugs slightly augment diuresis and are used in combination with loop diuretics or thiazides to decrease K^+ excretion (hence termed K^+ sparing). Both drugs act at the late distal tubule (or connecting tubule) to block the electrogenic transport of Na^+.
Uses: Because of their K^+ sparing properties, they are used in combination with loop and thiazide diuretics.

(6) Osmotic diuretics: Mannitol, Isosorbide and Glycerol.

These diuretics are pharmacologically inert substances which are filtered through the glomerulus, but not absorbed in the tubules. The unabsorbed solute in the tubular fluid exerts osmotic action, passive reabsorption of water in the proximal tubule is prevented (1 molecule of Mannitol withholds 6 molecules of water). This has secondary effect on Na^+ reabsorption, causing some Na^+ loss through urine. Therefore, Mannitol causes primarily a water diuresis, with relatively smaller natriuresis.

Mannitol is not absorbed orally, given i.v. as 5-10% solution @ 1-2 mg/kg.

Uses: Mainly used in acute renal failure to maintain GFR. e.g. Shock, severe trauma, cardiovascular surgery, haemolytic reactions etc. Also forced diuresis (in case of poisoning) and reduction of intracranial pressure (acute congestive glaucoma, head injury, stroke etc.).

(7) Xanthines: Theophylline.

It produces a mild transient diuresis. Mechanisms are – increased renal blood flow and GFR, but more importantly direct inhibition of tubular reabsorption. It is not used as a primary diuretic, but may augment response to other diuretics.

CHOICE OF DIURETIC:

Diuretics are relevant to all circumstances where body fluid volumes have increased either generally or locally. They are relevant whether the primary cause is trauma, infection, hypersensitivity or organ failure and are esp. valuable in the management of congestive heart failure.

The choice of agents is dictated by the speed, intensity and duration of response required.

- The loop diuretics act in minutes following i.v. injection and have a maximum effect, say 10 times greater than other classes, even acting when anuria is already present. Pulmonary oedema and immediate forced diuresis in the treatment of appropriate poisoning are two indications.
- Parenteral Acetazolamide is similarly effective for acute glaucoma.
- Where a moderate, more prolonged effect is required, as in chronic congestive heart failure, oral thiazides are appropriate.
- In shock with impending renal shut down, or for relief of cerebral oedema, intravenous osmotic diuretics are used.
- Where urinary pH change would increase the rate of excretion of a toxicant, increase antibacterial activity, or counter the formation of calculi, then acidifying or alkalinizing agents are indicated.
- Finally, for a mild, K^+ conserving effect or to counter hypokalaemia in long term thiazide or loop diuretic maintained patients, give potassium sparing diuretics in the therapeutic regimen.

URINARY ALKALIZERS

Examples – Sodium bicarbonate, sodium acetate and sodium citrate. Potassium salts are equally effective, but are potentially more toxic.

Urinary alkalizers are basic agents used for alkalinization of urine.

- Alkalinization of urine increases the antibacterial activity of aminoglycosides in urinary tract infections.
- The urinary alkalizers are of value during the administration of sulphonamides whenever there is the danger of crystalluria and damage to the kidneys as sulphonamides are more soluble in alkaline media.
- Bicarbonates are also able to increase the rate of excretion of salicylates and other weak acids by favouring their dissociation in ultrafiltrate.
- Alkalinization of urine is generally recommended to prevent the recurrence of cystine or urate stones in dogs after cystotomy.
- Dose – $NaHCO_3$ (Dog) = 0.5 to 1.0 gm tid with *ad lib.* water.

URINARY ACIDIFIERS

Examples – Sodium acid phosphate, ascorbic acid, methionine, chlorethamine etc.

These are drugs which cause acidification of urine. The effect of the drug is to deplete body base and increase body acid, and it is the compensatory renal adjustment which acidifies the urine.

Urinary acidification is undertaken for several reasons. It is a technique which can aid the excretion of basic substances by increasing their ionization in filtrate and thereby diminishing their passive reabsorption across the tubule wall.

Uses:

(i) Acidification improves the antibacterial activity of hexamine (methenamine), the penicillins and tetracyclines in the treatment of urinary tract infections; and may itself make conditions less conducive to bacterial growth.

(ii) Urethral obstruction in the cat can be treated by lavage with acidic solutions, as these dissolve the struvite component of obstruction.

Dose – Na acid phosphate – 0.15 to 0.3 gm tid

Ascorbic acid – 250 to 500 mg tid

Methionine – 30 mg/kg bid

Chlorethamine – up to 90 mg tid.

[**NB:** NaCl and Ammonium chloride also act as urinary acidifiers.]

URINARY ANTISEPTICS

These are drugs which exert antiseptic/ antibacterial action in urinary tract. The urinary antiseptics are alternatives to the sulphonamides and antibiotics and enable these agents to be restricted to use in life threatening conditions, and they can be used when bacterial resistance excludes the antibiotics.

Hexamine (Methenamine): It has an action of diuresis and urinary antiseptics, provided the pH of urine is below 5.5. For acidification of urine, Na acid phosphate is added. In acid urine, hexamine slowly decomposes and the formaldehyde exerts an antibacterial action.

Mandelic acid: The drug has antibacterial activity in urine at pH below 5.5. The mandelic acid salts are self acidifying, but additional acidification may be required.

Nitrofurantoin: In acid urine, it is effective against most urinary tract infections except *Pseudomonas* and *Proteus*.

Nitroxoline and Nalidixic acid: Action is not pH dependent.

ECBOLICS or Oxytocics

An ecbolic is an agent which stimulates contraction in the uterus at term, esp. in the treatment of atonic or hypotonic parturient uterus. Certain drugs have the ability to induce parturition before full term and are known as abortifacients. Ecbolics are used at term, usually when parturition has commenced. Their action is to increase the contractile activity of uterine muscle. There is overlap between ecbolics and abortifacients, and the distinction between them is in part dependent on use rather than action, e.g. the ecbolic ergot is capable of inducing abortion if given during pregnancy. All ecbolics should be used with great caution if the cervix is not fully dilated.

The use of ecbolics is indicated in the following:-

(i) During parturition when foetal position and presentation are normal and the cervix adequately dilated by the process of parturition, if prolonged.
(ii) For a flaccid post parturient uterus which is not contracting (involuting); and
(iii) For post parturient haemorrhage.

In all cases of uterine inertia or slow delivery, doses should be small and repeated. The different ecbolics that have therapeutic importance include Oxytocin, ergot alkaloids and prostaglandins.

OXYTOCIN:

It is the physiological oxytocic. It is produced in the neuronal bodies in the supraoptic and paraventricular nuclei of the hypothalamus and is stored in the posterior pituitary gland.

Release of Oxytocin: It is released by –

(i) Foetal and uterine stimuli at the time of parturition.
(ii) Vaginal stimulus during coitus.
(iii) Teat stimulus following suckling by the young one.

Effects of Oxytocin:

(i) During coitus, increases contraction of the genital tract facilitating the transport of sperms.
(ii) Terminates pregnancy if administered during pregnancy.
(iii) Converts weak, spontaneous and irregular uterine contractions into forceful, regular and purposeful contractions.
(iv) Causes milk secretion following teat stimuli by contracting the mammary myoepithelial cells, but does not increase milk formation.

Uses of Oxytocin:

[A] Obstetrical Uses:

(i) Aid to parturition in cases of uterine inertia (atonic or hypotonic parturient uterus).
(ii) Aid to post-parturient involution of uterus.
(iii) To induce uterine contractions following caesarean section to expel detached or loosened placenta.
(iv) In cases of retained placenta.
(v) To expel uterine debris in cases of metritis or pyometra and other uterine diseases.

Dose – Oxytocin is injected i.v. or i.m. @ 10-20 units in bitch, 25-50 units in ewe and sow and 75- 150 units in cow and mare.

[B] Milk let-down effect: To stimulate milk let down immediately after parturition in agalactic animals.

Dose – Oxytocin is injected i.v. or i.m. @ 5-10 units in bitch, 10-20 units in ewe and sow and 15-20 units in cow and mare.

The synthetic oxytocin analogues are –

- 1-deamino-oxytocin: It is many fold more potent than natural oxytocin.
- Arginine vasotonin: It is naturally occurring peptide found in the pituitary gland of many mammalian vertebrates. It has both oxytocic and antidiuretic actions.

ERGOT ALKALOIDS:

An ergot is a grain of rye grass which has become infected by the fungus *Claviceps purpurea.* Discovered as a cause of poisoning, the ergots were soon shown to contain many active principles in addition to their selection of ergot

alkaloids. Their ability to cause uterine contractions was soon recognized and was found to be especially the property of ergometrine (lysergic propanolamide). Ergometrine has some of the vasoconstrictor action of ergot alkaloids which cause gangrene of the extremities in cattle.

Ergometrine is no longer favoured during parturition because it sometimes causes a spasmodic contraction and so delays birth, but it remains of value in stage three of labour where the rapid onset and long duration of its vasoconstrictor and powerful uterine contracting actions secure rapid involution of the uterus and control of the post-partum haemorrhage.

Methylergometrine is an ecbolic even more powerful than ergometrine, but it lacks vasoconstrictor action.

PROSTAGLANDINS:

These also have a role in physiological parturition. They help in termination of prolonged pregnancy. There are so many synthetic $PGF_{2\alpha}$ analogues available for intramuscular use –

(i) Dinoprost (Lutalyse®)
(ii) Tiaprost (Iliren®)
(iii) Luprostinol (Prosolvin®)
(iv) Cloprostenol (Synchromate®)

TOCOLYTICS

The drugs which relax or inhibit the smooth muscles of the gravid uterus are called as tocolytic agents or uterine spasmolytics or uterine relaxants. The selective β_2 adrenoceptor agonists viz. Isoxsuprine, Salbutamol, Terbutaline, Ritodrine and Orciprenaline are the drugs used in human obstetrics. The tocolytics inhibit both the spontaneous and oxytocin induced contractions of the pregnant uterus. Their clinical applications include prevention of premature labour or to delay parturition for managemental convenience.

Isoxsuprine is administered at the dose rate of 0.5 mg/kg in all the species. The effect is seen within 15 minutes of injection and it lasts for 2 hours. The side effects may include tachycardia, peripheral vasodilation and muscle tremors.

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Chapter - 5

Fluid and Electrolyte Therapy

FLUID AND ELECTROLYTE THERAPY

FLUID THERAPY:

Fluid therapy consists of administration of isotonic fluids to correct body's imbalance. It is advocated in haemorrhages, vascular shock, anaemia, haemolysis, failure of blood clotting mechanisms and to provide specific antibodies against infections. The different fluids used are as follows:

1. **Whole Blood:** Intravenous infusion is done @ 20 – 40 ml/kg body weight. Cross matching is not necessary, except in horse and dog where there is no need of cross matching in the first instance, but subsequent transfusions need cross matching to prevent anaphylaxis.

   Repeated transfusions are probably safe if given within 24 hour, but after this time there is a considerable risk of antibodies formed against the foreign protein causing a reaction. If in doubt, always perform a cross-matching test.

   Blood for transfusion should be collected into a 3.8% Na citrate solution (one part of anticoagulant to 9 parts of blood), and should be used as soon as possible. The first 50 ml or so should be given slowly, with careful observation for signs of reaction. If it occurs, this is likely to appear first change in the character of respiration.
2. **Blood Plasma:** Intravenous infusion is done @ 15 – 20 ml/kg body weight. It is indicated when the body fluid component is lowered (normal cellular component) in conditions such as burns or dehydration.
3. **Blood Serum:** It is usually indicated for immunological purposes (intravenous administration of immune serum).
4. **Plasma Expanders/ Plasma Extenders/ Blood Volume Expanders/ Plasma Substitutes:** These may either be fluids obtained from blood or synthetic colloidal solutions which have osmotic characteristics approximating to that of plasma. These are capable of creating and maintaining an increase in circulating blood volume and may be used to correct plasma or blood loss although they are not able to replace lost oxygen carrying capacity. They constitute artificial fluids isotonic to the plasma.

   (a) Freeze dried plasma: This has been produced experimentally and used in calves and dogs. It has many of the advantages of the whole blood and is stable until made for use. It retains the protective γ-globulins of the donor, but also carries the risk of any virus infection in the donor animal being transmitted to the recipient. The risk can be minimized by prophylactic heat treatment.

   (b) Dextran:

   ☞ It is a branched polysaccharide prepared by growing a bacterium *Leuconostoc mesenteroides*, in a medium containing sucrose.

   ☞ Dextran is antigenic, but the large amounts infused seem not to cause antibody production.

- ☞ Infusion of dextran produces a volume expansion. Solutions of 6% and 10% concentrations are available in either saline or 5% dextrose.
- ☞ The dextran molecule slowly broken down into glucose, though some are excreted unchanged into urine.
- ☞ Dose: Dextran solutions are infused @ 10 – 25 ml/minute, 4 – 40 ml/kg body weight.

[NB: The volume of dextran solution injected should not exceed 1/3rd of body plasma volume (Plasma accounts for approx. 7.2% of body weight). If this proportion is exceeded, dextran has a heparin like action and severe haemorrhages may occur.**]**

(c) Polyvinylpyrrolidone (PVP):

- ☞ It is a complete organic polymer. It is no longer used as a volume extender as some remains in the cells of RE (reticuloendothelial) system for a very long time.
- ☞ PVP also cause release of histamine, which is disadvantageous.

(d) Gelatin polypeptide:

- ☞ 3.5 – 4% solution in isotonic electrolytes.
- ☞ It is non-antigenic and exerts no adverse effects on blood coagulation or cross-matching.
- ☞ Histamine release may occur on rapid infusion. (so, slow and intermittent infusion should be given).
- ☞ Degraded gelatin exerts a mild beneficial diuretic action.

(e) Hydroxyethylstarch or Hetastarch:

- ☞ It is similar to dextran in action.
- ☞ Antigenic, but no marked effect on blood coagulation.

ELECTROLYTE THERAPY:

It is administration of special electrolyte solutions to correct hypovolemia (dehydration/ haemorrhage), overhydration (renal, hepatic or cardiac diseases), electrolyte imbalance (hypocalcemia) and metabolic acidosis or alkalosis.

Specific electrolyte therapy is recommended as per the clinical condition. The different electrolyte solutions are as follows:

1. **Isotonic saline (Normal saline):**
   - ⌖ It is 0.9% w/v NaCl (more exactly 0.8775% w/v NaCl).
   - ⌖ It is the widely used replacement solution.
   - ⌖ Isotonic means 300 m.osmoL/L of fluid i.e. isotonic to plasma.
2. **Isotonic dextrose (Glucose 5%):**
   - ⌖ In reality, it serves to act as a source of water only, since the calorie content is very small, negligible in comparison with the maintenance requirements of an animal.
   - ⌖ To maintain a calf by isotonic dextrose, would need an impractical dose of 120 L/ day.
   - ⌖ Isotonic dextrose is therefore, most suitable for hyperosmotic states.

3. **Isotonic dextrose saline:**
   - The solution contains 0.18% NaCl plus 4.3% glucose.
   - Useful for maintenance of fluid and electrolyte levels.
   - Dose – 40 ml/ kg every 24 hourly.
   - The rapid metabolism of glucose means that this solution actually delivers water in excess of solute and is therefore indicated for hypertonic dehydration.
4. **Darrow's solution:**
   - It consists of 0.4% NaCl + 0.27% KCl + 0.58% Sodium lactate.
   - Used for treating metabolic acidosis associated with diarrhea and dehydration.
   - Sodium lactate is metabolized to $NaHCO_3$ and thus it has an alkalinizing effect.
   - It is potassium rich and therefore, counters the depletion of ICF (Intracellular Fluid) K^+ seen in severe dehydration.
5. **Compound Na lactate solution (Ringer's lactate or Hartman's solution):**
   - In addition to Darrow's solution, it contains Ca^{2+} ions and less of HCO_3^- and K^+ ions.
   - Indicated in dehydration linked with acidosis.
   - Each litre of solution contains:
     0.6 gm of NaCl
     0.3 gm of KCl
     0.22 gm of $CaCl_2$
     5 ml of 60% Sodium lactate.
   - Its composition closely follows the electrolyte concentrations of plasma except that HCO_3^- is provided as a precursor lactate.
6. **$NaHCO_3$ solution (1.5 – 5% solution):**
   - It is prepared where treatment of acidaemia is needed immediately without relying on metabolism of lactate to HCO_3^-, as it may take hours.
   - 1.5% solution is approximately isotonic with plasma.
7. **Gastric fluid replacement solution:**
   - ☞ It consists of 0.37% NaCl + 0.13% KCl + 0.374% NH_4Cl.
   - ☞ Indicated in cases of persistent vomition.
   - ☞ When persistent vomition has produced alkalosis, this solution can be used to correct the proton deficit, since NH_4^+ ion is metabolized to release H^+ ions.
   - ☞ The solution should be used with care, since NH_4Cl is toxic.

The volume of electrolyte solution to be administered (i.v.) is based on the severity of the condition. In severe dehydration/ hypovolemia, the replacement is to be done up to 15% of body weight (50 ml/kg/hr in severe cases or 15 – 30 ml/kg/hr in less severe cases). Ca^{2+} solutions need to be administered slowly, with caution, monitoring cardiac condition.

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Chapter - 6

Endocrine Pharmacology

ENDOCRINE PHARMACOLOGY

A hormone may be defined as a specific chemical synthesized and stored in specialized cells/tissues called endocrine glands. The hormones are released directly, in minute quantities, into the blood stream in response to internal needs and changes in external environment to coordinate a multiplicity of metabolic activities that maintain homeostasis within the body.

ADRENAL CORTICOSTEROIDS

The adrenal cortex produces (and releases without storing) steroid hormones which influence carbohydrate and electrolyte metabolism and small amounts of androgens. The major hormones are subdivided into two classes: the Glucocorticoids, whose actions are principally on carbohydrate but also protein and fat metabolism, and the mineralocorticoids which are responsible for regulating electrolyte and hence water balance.

The relevance of the adrenal cortex to therapeutics is that hypofunction produces Addition's disease, hyperfunction produces Cushing's syndrome and the Glucocorticoids, in pharmacological dosage, exert powerful gluconeogenic, anti-inflammatory and immunosuppressive actions.

FUNCTIONS OF CORTICOSTEROIDS:

(i) The mineralocorticoids act on the kidneys where they enhance the resorption of Na^+ and Cl^- and therefore of water, and increase the rate of loss of hydrions, K^+, phosphate and Ca^{2+}. The mechanism of action involves the synthesis of protein in the target cells, perhaps the sodium carrier itself. Sodium retention, oedema and hypokalaemia are features of Cushing's disease or of overdosing with those Glucocorticoids which possess mineralocorticoid action.

(ii) The Glucocorticoids influence carbohydrate (and protein) metabolism by increasing gluconeogenesis, i.e. the production of glucose from non-carbohydrate (protein) precursors by the deamination of amino acids. This leaves carbohydrate moieties and increases urinary nitrogen output. Glucocorticoids induced hyperglycaemia is accompanied by a decreased peripheral uptake or utilization of glucose and resistance to insulin, but liver glycogen stores are nonetheless replenished. Fat stores are also catabolized, as the presence of Glucocorticoids favours lipolysis. The glycerol thus made available also contributes to gluconeogenesis. The end effect of long term steroid administration is muscle wasting and a redistribution of fat, exemplified by the "moon face" and "buffalo hump" or Cushing's syndrome in man, accompanied by bone thinning due to protein resorption and decreased calcification.

(iii) Corticosteroids sensitize vascular smooth muscle to noradrenaline and maintain normal capillary permeability and myocardial contractility.

(iv) Glucocorticoids exert anti-inflammatory and immunosuppressive effects, which are generally regarded as pharmacological effects of Glucocorticoids, and shared by NSAIDs. These effects are due to the formation and release of an array of mediators. These effects may also be credited to physiological role of glucocorticoids, checking the 'overshoot' of body's powerful defense mechanisms.

- Reduction in formation of mediators such as prostaglandins, leucotrienes, platelet activating factor (PAF), interleukins, tumour necrosis factor (TNF), cell adhesion factor, plasma complement components, nitric oxide and IgG due to suppression of specific genes transcription. Also suppresses histamine release from basophils.
- Inhibition of vasodilatation and formation of oedema, inhibition of neutrophil migration and macrophage function, proliferation and action of T-helper cells, suppressed fibroblast function, reduced production of collagen and glycosamonoglycans (reduced progress of chronic inflammatory or healing or repair). Tendency for development of osteoporosis may also occur due to suppressed action of osteoblasts and increased action of osteoclasts.

The above effects are due to interaction of glucocorticoids with intracellular steroid receptors and modification of gene transcription, inducing synthesis or suppression of specific proteins (enzymes).

The biosynthesis of glucocorticoids is inhibited by **metyrapone** which can be used as a diagnostic test to assess ACTH secretion. **Aminoglutethimide** and **ketoconazole** (antifungal agent) also inhibit steroidogenesis. These drugs can be used in treating Cushing's syndrome.

PRINCIPLES OF CORTICOSTEROID THERAPY:

1. Dosage schedule must be according to individual cases and should meet the requirement of replacement to the physiological levels. Higher doses result in atrophy of adrenal cortex and permanent hypofunction of the gland. When prolonged therapy is required, small doses are selected. Therapy must also be withdrawn gradually.
2. Corticosteroids do not cure the diseases (inflammations), but give relief due to anti-inflammatory effects. [It should be stressed that corticosteroids (other than replacement therapy) are palliative rather than curative. This means that symptoms will reappear, unless the primary cause has resolved or been adequately treated, when steroid dosing ceases].
3. Should be avoided during active infections, unless compulsory. If used, the microbes may spread over extensive areas (inhibition of natural tissue barrier processes). Use in microbial diseases must be accompanied by high doses of antibiotics.
4. For chronic affections, esp. joint pains, conjunctivitis, dermatitis, pruritis etc. local application should be preferred. (Systemic use may cause other effects and atrophy of the gland).
5. Should not be used simultaneously with immunization/ vaccination schedules.

6. Should be contraindicated in the following conditions:
   (i) Diabetes mellitus – as glucocorticoids induce insulin resistance.
   (ii) Hypertension – as glucocorticoids induce hypertension in animals and human beings through activation of renin-angiotensin system, reduced activity of hypotensive kallikrein-kinin system, PGs, EDRF, NO etc.
   (iii) Renal insufficiency – No glucocorticoid given in large doses is completely devoid of mineralocorticoid (salt retaining and K^+ losing) activity, therefore, excessive use may precipitate or exacerbate hypertension and induce hypokalaemia.
   (iv) Late pregnancy – Late pregnancy is an obvious contraindication esp. for C-16 methylated corticosteroids, except in pregnancy toxaemia where recovery often follows abortion. In early pregnancy, foetal abnormality may be found.
   (v) Corneal ulcers –
      - Recent major surgery exemplifies a situation where delayed wound healing could be disastrous.
      - Deep corneal ulceration can readily progress to penetration under steroids.
   (vi) Hepatic insufficiency – Glucocorticoids induce a form of micronodular cirrhosis. At the same time, there may be hepatopathy and hepatomegaly.

CLINICAL USES OF CORTICOSTEROIDS:

1. **Ketosis:** A major use for glucocorticoids in dairy practice is in the treatment of bovine ketosis. The simple disease is characterized by hypoglycaemia, elevation of blood ketone concentrations, depression, loss of appetite and decrease in milk yield. Despite the presence of normal levels of plasma corticosteroids, exogenous glucocorticoids reverse these symptoms. Blood sugar rises due to gluconeogenesis from amino acids and/or reduced peripheral utilization of glucose, liver glycogen levels increase, and so the previously depressed levels of citric acid cycle intermediates. Blood ketone level returns to normal over a few days, appetite returns and milk yield picks up after a short delay.
   Drug and dose: Betamethasone and Dexamethasone – upto 30 mg. i.m.
   Triamcinolone (Vetalog®) – very much effective against ketosis.
   LA – 5 ml i.m.
   Prednisolone – LA- 10 ml i.m.
2. **Pregnancy toxaemia in ewes.**
3. **Stress:** A major physiological role for the steroids is that of increasing the ability of the body to resist the stresses of trauma, disease, environment, emotions, fatigue etc. It is argued, therefore, there is a case for using a glucocorticoid as an adjunct to therapy in any situation in which an element of stress exists. e.g. Shock, tissue damage, allergy or toxaemia.
4. **Anti-inflammatory effect:**
   Cattle – Mastitis, lameness.
   Horse – Lameness (due to joint injury or arising from swollen bursae or tendon sheaths), conjunctivitis.

Dogs – Arthritis, dermatitis, eczema, pruritis, conjunctivitis, iridocyclitis or acute anterior uveitis (increased proliferation of cells and protein in anterior chamber of eye, causing low intraocular pressure, conjunctiva hyperaemia, iridal swelling, photophobia etc.).

5. **Induction of parturition:** Administration of a single dose injection of dexamethasone (10-30 mg), betamethasone (20-30 mg) or flumethasone (5-10 mg) to a cow in late pregnancy is followed by parturition within 72 hours. Unfortunately, these induced parturitions are accompanied by a very high incidence of retained placenta and there is an increase in calf mortality to about 15%. For these reasons, the technique remains more of an oddity than a commercially viable practice. It is effective in the ewe after 130 days without placental retention and this action has been demonstrated in the nanny and mare also.

NB:

In response to foetal ACTH
↓
Foetal adrenal secretes cortisol
↓
Acts on placenta modifying its endocrine activity
↓
Placental progesterone output falls, while estrogen & $PGF_{2\alpha}$ output increases
↓
These changes make the uterine muscle more responsive to stimulation by oxytocin and $PGF_{2\alpha}$.

Apart from the above mentioned uses, glucocorticoids are also used in physiological replacement therapy, intensive term and shock therapy, immunosuppressive therapy and neoplasia.

DOSES AND ADMINISTRATION OF CORTICOSTEROIDS:

(i) Prednisolone and products with similar activity:

LA – 100 to 200 mg i.m. daily.

SA – 2 to 20 mg i.m. initially followed by oral therapy (dog – 0.5 to 1 mg/kg daily by mouth, cats – 1 mg/kg daily by mouth).

(ii) Dexamethasone and products with similar activity:

Parenteral – Horse, cattle – 10 to 30 mg
Foal, calf, sheep, goat, pig – 2 to 5 mg.
Dog – 0.5 to 2 mg
Cat – 0.25 to 2 mg.

Oral – SA – 0.25 to 2 mg.

These daily doses should be divided whenever possible. Initial doses may be maximum or near maximum, but once symptoms are controlled, doses should be reduced to the minimum effective. The quoted doses are guideline figures only and should be in each case be adjusted according to the circumstances.

THE ENDOCRINE PANCREAS

The pancreas, which lies in the loop of duodenum, contains two vastly different types of glandular tissue. The greater part of the gland is exocrine and secretes a fluid rich in digestive enzymes, via the common bile duct, into the small intestine. Dispersed throughout the mass of the exocrine gland are the Islets of Langerhans whose β-cells secrete the stored polypeptide hormone insulin, in a rapid response to GI peptide hormones, plasma concentrations of glucose, amino acids or fatty acids, and other local (glucagon) or systemic (ACh and β agonists) chemical messengers or drugs (sulfonylureas).

Glucagon is a smaller, single chain polypeptide secreted by the Islet α_2-cells. In that, it has glycogenolytic and gluconeogenetic effects, its actions oppose those of insulin. The α_1-cells release somatostatin, the growth hormone release inhibiting factor found also in the hypothalamus. Glucagon, growth hormone and insulin are of central importance to the regulation of intermediary metabolism.

INSULIN:

INJECTION OF INSULIN:

1. Generally, it is the sterile antidiabetogenic hormone of the pancreas of either the **pig or the ox**, appropriately purified. It is a clear, colourless liquid, standardized by bioassay to contain 20, 40 or 80 units of activity in each milliliter. Insulin from different sources has a potency in the range of 20-80 units/ml.
2. The rate of absorption of insulin and its duration of action depends upon the physical state (crystalline or amorphous, proportion of zinc, solution or suspension) and the route of injection of the chosen formulation.
3. The complexed suspension i.e. protamine zinc insulins and globin zinc insulins (40 or 80 units/ml) are effective for about 48 hour and 24 hour, respectively, but the plain (crystalline or regular) injection is effective for a period of only about 8 hour and requires injection twice a day.
4. **Lente Insulins:** The lente (means slow) insulins are preparations of insulin with increased amounts of zinc incorporated in their crystals to reduce the solubility of the insulin in body fluids, and so at the expense of some delay in onset, to give a period of action intermediate between that of plain insulin and the protein complexed-material. Lente insulins are well suited to once daily injections, having an 18-24 hour duration of action after s.c. injection.
5. The hormone (MW 5700) is a polypeptide composed of two straight, cross-linked chains of 21 and 30 residues per chain. There are some minor interspecies sequence variations: the commercial product was of porcine or bovine origin but is now obtained from **genetically engineered *Escherichia coli***.

MECHANISM OF ACTION:

(i) After binding to specific cell membrane-located receptors, insulin increases the rate of entry of glucose, amino acids and potassium ions into most cells. This reverses the hyperglycaemia of diabetes mellitus by allowing excess glucose to become intracellular.

(ii) Inside the cell, protein synthesis is increased and glucose is phosphorylated by ATP and hexokinase and is used to derive energy or for incorporation into glycogen.

(iii) The storage of carbohydrate is further aided by the inhibition of the action of the enzymes of glycogenolysis.

(iv) Protein synthesis is aided by the impairment of gluconeogenesis.

(v) Insulin also facilitates fat deposition and strongly inhibits lipolysis.

NB: ☞ Insulin release is effected by –

- ✓ Hyperglycaemia
- ✓ In response to amino acids, free fatty acids, ACTH, GH, c-AMP, GI peptide hormones etc.

☞ Insulin, growth hormone and steroid hormones are anabolic in effect.

☞ Glucocorticoids, thyroid hormones, glucagon and catecholamines are catabolic in effect, and exert actions opposite to those of insulin on glucagon synthesis, nitrogen balance and deposition of fat.

USES:

In true diabetes mellitus in dog –

The condition is very much similar to that which occurs in man; hyperglycaemia and glycosuria are the dominant clinical features; ketones are also found in the urine and blood. Sugar present in the blood in large quantities, is obtained from various sources – absorption from the intestine, mobilization of carbohydrate reserves, and breakdown of fat and protein. The metabolism of fat is incomplete and results in the elevation of plasma free fatty acid concentration, the formation of ketones and the provision of glycerol. The availability of amino acids is increased, partly from protein catabolism and gives rise to glucose after deamination in the liver.

The unproductive drain on carbohydrate, protein and fat reserves is directly or indirectly responsible for other diagnostic symptoms: increased appetite and thirst, emesis and diarrhoea, increased urine production, and a progressive emaciation with marked muscle wasting and lethargy. Bilateral cataract occurs occasionally and wounds are slow to heal.

Insulin injections reduce the blood glucose level considerably both by hepatic glycogenesis and by increasing tissue breakdown of sugar, releasing energy. Glycosuria ceases when the blood sugar concentration falls below the renal threshold. Ketone production ceases and the breakdown of proteins and fats is reversed. In acetonaemia in cattle and pregnancy toxaemia in sheep, insulin has been used in conjunction with glucose therapy.

ORALLY ACTIVE HYPOGLYCAEMIC AGENTS:

SULFONYLUREAS:-

(i) These are the hypoglycaemic sulfonamides.

(ii) The mode of action of these drugs is a direct stimulation of the secretory activity of pancreatic β-cells plus a sensitization of target cells to receptors.

(iii) Sulfonylureas can not alter blood glucose concentrations in **pancreatectomized and juvenile (type-I)** animals suggesting that sulfonylureas stimulated the pancreas to stimulate insulin synthesis.

(iv) Indeed sulfonylureas have become a major therapeutic agent used to treat type II diabetes in human until recently.

Type-I (Insulin dependent or juvenile onset diabetes mellitus) – There is β-cell destruction in pancreatic islets. In all type-1 cases, circulating insulin levels are low or very low and patients are more prone to ketosis. This type is less common and has a low degree of genetic predisposition. Type –I is of 2 types i.e. autoimmune and idiopathic type.

Type-II (Non-insulin dependent or maturity onset diabetes mellitus) – There is no loss or moderate reduction in β-cell mass. Insulin in circulation is low, normal or even high. Has a high degree of predisposition and generally has a late onset (past middle age). Over 90% cases are of type II diabetes mellitus.

(v) **Tolbutamide** is a short acting member of the group and **chlorpropamide** is a long acting (because it is not metabolized).

(vi) The sulfonylureas have not proved effective in the dog, probably because the diabetes is generally too severe by the time of consultation.

(vii) Furthermore, the sulfonylureas and another group of oral hypoglycaemics, the biguanides, are rather toxic, and their use in man remains under review. Their particular merit is the convenience of oral administration.

SEX HORMONES

The gonads produce steroidal hormones which have androgenic, estrogenic and progestational activities. Their synthetic analogues have similar or antagonistic actions and form a very important class of drugs.

ANDROGENS:

These are substances which cause development of secondary sex characters in the castrated male.

Natural Androgens:

1. Testosterone
2. Dihydroxytestosterone (more active form of testosterone).
3. Dehydroepiandrosterone
4. Androstenedione

} Weak androgens (potency 1/20 to 1/30)

5. Androsterone – It is a metabolite of testosterone which is excreted in urine. It has 1/10th the activity of testosterone.

Synthetic Androgens: Orally active

1. Methyltestosterone
2. Fluoxymesterone
3. Testosterone undecanoate
4. Mesterolone

Actions of androgens:

(i) Sex organs and secondary sex characters (androgenic):
- ✓ Growth of genitals – Penis, scrotum, seminal vesicles, prostrate.
- ✓ Growth of hair – pubic, axillary, beard, moustache, body hair and male pattern of its distribution.
- ✓ Thickening of skin, increased activity of sebaceous glands, loss of subcutaneous fat resulting into veins looking prominent.

(ii) Testes – Normal spermatogenesis and maturation of spermatozoa.

(iii) Skeleton and skeletal muscles (Anabolic) – Responsible for the pubertal spurt of growth in boys and to a smaller extent in girls.

(iv) Erythropoiesis – Accelerates erythropoiesis.

Pharmacokinetics:

Testosterone is inactive orally. Intramuscular injection of testosterone is also of short duration.

Metabolites of testosterone – Androsterone and etiocholanolone.

Plasma $t_{1/2}$ of testosterone = 10-20 minutes.

Synthetic androgens (methyltestosterone and fluoxymesterone) are metabolized slowly and have a higher duration of action.

Uses:
- ✓ Testicular failure, Hypopituitarism, AIDS related muscle wasting,
- ✓ Teaser bulls – Testosterone treated cows were as effective in oestrous detection as surgically altered bulls.

ANABOLIC STEROIDS:

These are synthetic androgens with supposedly higher anabolic and lower androgenic activity. Anabolic **:** androgenic activity ratio of testosterone is 1. Compounds with ratio greater than 1 are called anabolic steroids.

Examples - **Trenbolone acetate** (weak androgenic activity and greater anabolic action) - Only anabolic steroid used in cattle for growth promotion.

Nandrolone
Oxymetholone
Stanzolol
Methandienone
} Not commonly used for growth promotion.

Uses:

(i) Growth promotion – Only trenbolone acetate (TBA) is used for growth promotion in cattle and to a lesser extent sheep, but not in pigs or horses. Subcutaneous implantation in the ear of cattle is done for administration of the drug.

Enhancement of physical ability in athletes – When administered during the period of training, anabolic steroids can increase the strength of exercised muscles. However, effects are transient, and contrary to popular belief, there is no scientific evidence that performance is enhanced. This is considered an abuse and anabolic steroids are included in the list of "dope test" performed on athletes before competitive games.

ANTIANDROGENS:

1. **Delmadinone –** Recommended for the control of hypersexuality in male cats and dogs and for relieving prostatic hypertrophy.
2. **Cyproterone –** It is a derivative of progesterone and is a competitive antagonist of dihydrotestosterone. It is used in the treatment of male sex offenders.

ESTROGENS:

These are substances which can induce estrous in spayed animals.

Natural Estrogens:

1. Estradiol – Major estrogen secreted from ovary. Most potent.
2. Estrone – Estradiol is oxidized in the liver to estrone.
3. Estriol – Estrone is hydroxylated to form estriol.
4. Equilin – $1/5^{th}$ estrogenic potency of estradiol.

Synthetic Estrogens: Natural estrogens are inactive orally and have a short duration of action.

1. Steroidal estrogens – Ethinylestradiol, mestranol, tibolone.
2. Non-steroidal estrogens – Diethylstilbestrol (Stilbestrol) – Used orally.
   Zeranol – Analog of naturally occurring plant estrogen Zearalenone.

Actions of estrogens:

(i) Sex organs: Bring about pubertal changes – growth of uterus, fallopian tubes and vagina etc.

(ii) Secondary sex characters: Development of mammary gland, pubic, axillary hair, feminine body contour, behaviour etc.

(iii) Metabolic effects: Estrogens are anabolic similar to but weaker than testosterone.

(iv) Important in maintaining bone mass: Primarily by retarding bone resorption. Osteoclast pit formation is inhibited and there is increased expression of bone matrix such as osteonectin, osteocalcin and alkaline phosphatase etc.

Pharmacokinetics:

Natural estrogens are inactive orally.

Estradiol esters injected intramuscularly are slowly absorbed and exert prolonged action.

Ethinylestradiol: is metabolized very slowly ($t_{1/2}$ = 12-24 hour) orally active and more potent.

Uses:

(i) Hormone replacement therapy (HRT): To avoid –

- Vasomotor disturbances – Hot flushes, chilly sensation, inappropriate sweating etc.
- Urogenital atrophy.
- Osteoporosis – Fractures esp. of femur, radius, vertebrae etc.
- Dermatological changes – Thinning, drying and loss of elasticity of skin, wrinkles, thin and listless hairs.
- Psychological disturbances – Irritability, depressed mood, loss of self confidence, anxiety etc.
- Increased risk of cardiovascular diseases – Coronary artery disease, myocardial infarction, stroke etc.

Estrogen HRT is highly efficacious in suppressing the menopausal syndrome.

(ii) Growth promotion in animals: Estradiol increases nitrogen retention, growth rate by 10-20% in steers, lean meat content by 1-3%; and feed efficiency by 5-8%. Estradiol can be used in steers, to best advantage, but has some anabolic effects in heifers and veal calves. Estradiol works best in lambs in conjunction with androgens and is not effective as an anabolic agent in pigs.

(iii) **Induction of lactation in cow:** This procedure is performed in order to salvage milk from sub-fertile dairy cows. It should be recognized that drugs (Estradiol 17β, progesterone, dexamethasone and reserpine) used in induction of lactation may temporarily interrupt ovarian function and result in prolonged periods of estrous. Reserpine is used to stimulate prolactin secretion and has resulted in greater milk yields.

Doses:

Estradiol 17β (500 mg)
Progesterone (1000 mg) } Via an impregnated sponge. The sponge to be left for 10 days (Intravaginal).

After 6 days, dexamethasone (20 mg) i.m.

Reserpine (2.5 mg) – i.m. given on 6, 8 and 10th days after sponge insertion.

Success rate = 96%.

ANTI-ESTROGENS:

1. **Tumoxifen:** It is an antiestrogen used in the treatment of estrogen dependent breast cancer in woman.
2. **Clomiphene** and **Cyclofenil:** These are also antiestrogens, which inhibit estrogen binding to hypothalamus and anterior pituitary preventing normal feedback of estrogens, causing excess secretion of GnRH and of gonadotrophins resulting in increased estrogen secretion and ovulation. Their antiestrogen effect results in induced ovulation. These drugs are used to treat lack of ovulation in infertile women.

PROGESTINS:

These are substances which convert the estrogen primed endometrium to secretory and maintain pregnancy in animals spayed after conception. (Progestin = favouring pregnancy).

Natural progestins:

(1) Progesterone (21-C Steroid, $t_{1/2}$= 5 to 7 minutes)
(2) Hydroxyprogesterone caproate (Longer acting injection).

Synthetic progestins:

(1) Megesterol acetate
(2) Dihydrogesterone
(3) Medroxyprogesterone acetate (weak androgenic)
(4) Mibolerone
(5) Melengesterol acetate (MGA)- Orally active, Used to suppress estrogens in fattening female cattle.
(6) Proligestone

Actions of Progesterone:

(i) Uterus: brings about secretory changes in estrogen primed endometrium, hyperaemia, tortuocity of glands etc. Decreases sensitivity of myometrium to oxytocin.
(ii) Cervix: Converts the watery cervical secretion to viscid – Mucosal plug.
(iii) Mammary gland: Proliferation of acini of mammary gland, and in combination with estrogen it converts udder for milking.
(iv) CNS: High circulating level of progesterone (during pregnancy) appears to have a sedative effect.
(v) Body temperature: It causes a slight (0.5°C) rise in body temperature restoring the hypothalamic thermostat.
(vi) Pituitary: Progesterone is a weak inhibitor of gonadotrophin secretion from pituitary. It decreases the frequency of LH pulses by action on hypothalamic pulse generator. So, suppresses ovulation.

Uses:

1. As contraceptives (Human).
2. HRT – Along with estrogen, progesterone is also given in HRT for few days to avoid chances of endometrial carcinoma.
3. Threatened or habitual abortion
4. Postponement of estrous in bitches: Megesterol acetate, mibolerone.
5. Induction of lactation in the cow.
6. Synchronization of estrous cycle

ANTI-PROGESTINS:

These anti-progestins may act as abortifacients.

Mifepristone: (A progesterone antagonist) – Along with a prostaglandin derivative proved to be very effective in terminating early pregnancy in woman.

THYROID HORMONES

The thyroid gland secretes three hormones – thyroxine (T_4), triiodothyronine (T_3) and calcitonin. The former two are produced by thyroid follicles, have similar biological activity and the term "thyroid hormone" is restricted to these only. Calcitonin is produced by interfollicular 'C' cells is chemically and biologically different.

Chemistry and synthesis of Thyroid hormones:

Both T_4 and T_3 are iodine containing derivatives of thyronine, which is a condensation product of two molecules of amino acid tyrosine.

Thyronine = Tyrosine + Tyrosine
T_4 = 3,5,3',5'-tetraiodothyronine
T_3 = 3,5,3'-triiodothyronine

The thyroid hormones are synthesized and stored in the thyroid follicles as part of thyroglobulin (TG) molecule.

Steps in synthesis and release:

(i) *Iodine uptake*: [Blocked by thiocyanate, perchlorate & cardiac glycosides].
Thyroid follicular cells have an active transport process (Na^+:I^- symporter) to concentrate iodide in them.

(ii) *Oxidation and iodination*: [Blocked by thiourea and thiouracil].
I^- trapped by follicular cells is oxidized by peroxidase enzyme with the help of H_2O_2 to iodinium (I^+) ions or hypoiodous acid (HOI). These forms of iodine combine quickly with tyrosil residues of thyroglobulin (TG) to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).
Iodinium (I^+) + Tyrosil residue of TG = MIT & DIT

(iii) *Coupling*:
MIT + DIT = T_3
DIT + DIT = T_4

(iv) *Storage and release*:
Tyroglobulins containing iodinated tyrosil and thyronine residues are transported to the interior of the follicles and remains stored as thyroid colloid till it is taken back into the cells by endocytosis and broken down by lysosomal proteases. The T_4 and T_3 so released is secreted into circulation while MIT and DIT residues are deioninated and the iodide released is reutilized.

(v) *Peripheral conversion of T_4 to T_3*:
Liver and kidneys convert T_4 to T_3. About $1/3^{rd}$ of T_4 secreted is converted to T_3. T_3 is 5 times more potent than T_4, although T_4 is secreted in much excess.

[**NB:** Thyroid stimulating hormone (TSH) or thyrotropic hormone regulates all stages of this process from iodide uptake to the final discharge of T_3 and T_4.]

Actions of Thyroid hormones:

1. Growth and development:
   Cretinism – Congenital deficiency of T_4 and T_3 (Mental retardation).
   Myxoedema – Adult hypothyroidism.
   Graves' disease – Hyperthyroidism.
2. Intermediary metabolism:
   Lipid – Lipolysis
   Carbohydrate – Glycogenolysis, gluconeogenesis.
   Protein – Overall negative nitrogen balance, wasting condition, weight loss.
3. Calorigenesis: T_3/T_4 increase BMR by stimulation of cellular metabolism.
4. CVS: Cause hyperdynamic state of circulation.
5. Nervous system: Cretinism (Mental retardation), Graves' disease (Anxious, nervous, excitable condition and exhibit tremors and hyperreflexia.)
6. GIT: Propulsive activity is increased.
   Hypothyroidism – Constipation
   Hyperthyroidism – Diarrhoea.
7. Haemopoiesis: Maintains normal haemopoiesis.

Preparations of Thyroid hormones:

1. L-Thyroxine sodium:
   ☞ Laevo form is twice as much active than the racemic mixture.
   ☞ Maximum effect is produced in 10 days.
2. Liothyronine soiium (T_3):
   ☞ Maximum effect is produced in 1-2 days.
   ☞ Less chances of cumulation.

ANTITHYROID SUBSTANCES:

1. **Natural Goiterogens:** Goitrin (Certain plants of genus *Brassica*, such as cabbage, turnip etc. contain a compound goitrin which has antithyroid activity).
2. **Thioureylenes (Thionamides):** Propylthiouracil, Methimazole, Carbimazole.
3. **Non-thioureylene antithyroid agents:** Ipodate, Radioactive iodine (I^{131}).

Antithyroid substances find occasional use in the treatment of hyperthyroidism.

✷ ✷ ✷ ✷ ✷

Chapter - 7

Drugs acting on Skin & Mucous Membranes

DRUGS ACTING ON SKIN & MUCOUS MEMBRANES

ADSORBENTS & PROTECTIVES:

These are finely powdered, inert, insoluble solids capable of inactivating the irritants by binding to them. They exert physical protection to skin or mucous membranes.

Adsorbents act by binding gases, toxins and some organisms (such as bacteria) to prevent exposure to the damaged skin surface.

Protectives function by providing an occlusive layer of protection from the external environment or by providing mechanical support to the affected area.

Protectives and adsorbents can further be divided into two subclasses:- Dusting powders and Mechanical Protectives.

Dusting Powders: are generally inert and innocuous substances. e.g. Starch, $CaCO_3$, Talc, Titanium dioxide, ZnO & Boric acid.

Mechanical Protectives: provide an occlusive film that protects the underlying skin from irritants present in external environment (UV radiation, contact irritants, toxins etc.), provide mechanical support and are popular vehicles for many drugs. e.g. Kaolin, Lanolin, Anhydrous lanolin, Mineral oil, Olive oil, Peanut oil, Petroleum, Zinc stearate etc.

DEMULCENTS:

Demulcents are generally high molecular weight compounds that are water soluble and function by alleviating irritation ('*demulcere*' means to smooth). These are inert substances which sooth and relieve irritation, primarily involving the inflamed/ injured mucous membranes. They form a protective layer over the irritated surfaces. e.g. Glycerine, Propylene glycol, Solution of gum acacia, Gum tragacanth etc.

EMOLLIENTS:

These are bland (mild, gentle) fatty materials often used to soften or moisten the skin. These are primarily useful when treating skin conditions resulting from water soluble irritants and air borne bacteria because of their ability to act as a protectant sequestering the damaged skin away from these noxious stimuli. When used topically, emollients soften skin by decreasing transepidermal water loss or transpiration and increasing the hydration of the stratum corneum. A recent addition to this class is silicone based polymers such as **dimethicone**. Therefore, this is a useful group of compounds for treating dermatologic conditions involving dry, crusty or flaky lesions of the epidermis. Emollients are used today as vehicles for many lipid soluble drugs.

Vegetable Oils: Olive oil, Cotton seed oil, Corn oil, Almond oil, Peanut oil, Persic oil, Cocoa butter.

Animal fats: Lanolin (wool fat with water added), Anhydrous wool fat (no water added), Lard, Whale oil.

Hydrocarbons: Paraffin, Petroleum (white petroleum – vaseline), Mineral oil, White/ yellow waxes (bees wax), Spermaceti.

ASTRINGENTS:

Astringents are agents that precipitate protein, toughen the skin, promote healing and dry the skin when applied topically. When used to coagulate blood, astringents are said to be **styptic** and elicit a mildly uncomfortable sensation when applied to small open wounds. Most of the chemicals in this group are inorganic salts of Al, Zn, K and Ag and include $AlCl_3$, $Al_2(SO_4)_3$, Calamine (a combination of Fe_2O_3+ZnO_2), $KMnO_4$, $Ag_3(NO_3)_2$, $ZnCl_2$, ZnO, Zirconium chlorhydrate and tannic acid.

They are mainly germicidal agents that have also astringent activity. Other astringents are of vegetable origin, most of these preparations owing to their activity to tannic acid (gallotannic acid). Astringents in the vegetable - derivative group include gallic acid, kino, krameria & rubus (blackberry). Astringents have limited uses in veterinary medicine today.

G.I. MUCOSAL PROTECTANTS:

These are agents which protect the intestinal mucosa against irritation by forming a protective layer, neutralizing the irritants or absorbing the irritants. e.g. Kaolin, activated charcoal, bismuth carbonate etc.

COUNTERIRRITANTS:

These are agents used to produce hyperaemia in an attempt to relieve pain and promote healing of tissues beneath skin after application over the surface (skin). The reasoning which prompts their use is in that where a chronic inflammation exists, a counterirritant will cause an over-riding acute inflammation with a great increase in vascularity and, consequently, an increased blood supply to the area. This increased blood supply results in a greater concentration of blood-borne anti-disease factors such as leucocytes, increased nutrition and an improved removal of waste products by the venous and lymphatic systems. It is hoped that when this acute inflammation subsides the cause and some of the results of the chronic inflammation will also have been removed. Three stages of counter-irritation are distinguishable:--

(1) A rubefacient action: When the counter-irritant applied causes only mild irritation and a small increase in congestion – literally translated the term means "to make red". Rubefacients often have pain relieving or anodyne properties which may be due either to some pharmacological action of the drug or to the creation of a diversionary sensation. Iodine, camphor, methyl salicylate, turpentine and ammonia are all rubefacients.

(NB: Heat applied to the skin via a hot water bottle, heat lamp, moist hot pack or an electric heating pad are acceptable rubefacients and are extensively used in human medicine. Kaolin poultice – is a method of applying heat to a localized area.**)**

Chemical rubefacients are more commonly used in veterinary medicine mainly due to the difficulty in applying the heat source for extended lengths of time.

(2) Vesication: It occurs when the irritation is severe; this damages the capillary system and results in serous exudates collecting in the superficial skin layers to form blisters. This is the origin of the common name for vesicant dressings – "blisters". Mercuric iodide and cantharide ointments are the preparations most frequently used for blistering.

Cantharides: These are obtained from the dried beetles (Spanish fly) and contain cantharidin. Ointments containing 0.01 – 0.16% of cantharidin are used to cause blisters. "Blistering" is used to treat tendon injury in horses, being a mild and more acceptable treatment than firing.

Mercuric iodide (Red iodide of mercury): It is a commonly used blister when made in a base of lard or soft paraffin. It is used in concentrations of 2 – 10%, and following rubbing of this ointment on skin for 5 – 10 minutes, blistering follows after a few hours. Whenever, a blistering agent is used, care must be taken to protect surrounding tissue by application of zinc oxide ointment.

(3) Pustulation: Pustulation is the third stage, where the irritation is so great that the deep layers of the skin are damaged and the blisters become filled, not with serous exudates, but with the products of cellular destruction – pus. As the deeper layers of the skin are damaged, including the malpighian layers, the ability of regeneration is lost and scar tissue is formed which when it contracts, may limit the action of joints or tendons and at best cause permanent blemishes (mark, scar). It follows that no substance should normally be applied in a manner or form capable of causing irritation beyond the stage of vesication. Examples of pustulants – Strong ointment of red iodide of mercury (25%), Cantharidin ointment (12%).

KERATOLYTICS, KERATOPLASTICS & ANTISEBORRHEICS:

Keratolytics function by loosening keratin, which facilitates the desquamation of stratum corneum, whereas keratoplastics attempt to normalize keratinization by slowing basal cell proliferation through inhibition of DNA synthesis. Other mechanisms may also contribute to this effect. Antiseborrheics attempt to modulate sebum production in the skin. Many of the keratolytics are also keratoplastics and/ or antiseborrheic, therefore, these functions are discussed together. Examples of keratolytic, ketaoplastic and antiseborrheic agents:-

(i) Salicylic acid (2-hydroxybenzoic acid):

- Used topically as keratolytic, keratoplastic and antiseborrheic agent and has some mild antibacterial and antifungal actions.
- Salicylic acid (2 – 10%) causes the dead or dying cells of the stratum corneum to hydrate, swell and soften, thereby hastening their desquamation, and solubilizes the intercellular lipid layer, releasing the cells of the stratum corneum from each other.
- Salicylic acid ointment is used in hyperkeratosis (a solution containing 40% antimony trichloride + 5% salicylic acid or 3 – 5% salicylic acid in alcohal). A solution of 10 – 20% salicylic acid in alcohol is used for dissolving corns.

(ii) Benzoyl peroxide:

- It is metabolized to benzoic acid by the viable epidermal cells during penetration.
- Keratolytic, antiseborrheic, strong oxidizer, free radical generator (and so have some bactericidal actions).

(iii) Resorcinol (m-dihydrobenzene):

- Keratolytic agent having some bactericidal and fungicidal properties. Precipitates protein like urea. Promotes hydration of keratin, resulting in its keratolytic function.

CAUSTICS & ESCHAROTICS:

Caustics (also known as corrosives) are agents that destroy tissue after one or more applications. Escharotics (also known as cauterizers) are corrosive and will also precipitate proteins leading to the formation of a scab and eventually a permanent scar. Caustics have been used to induce desquamation of the stratum corneum (keratolytic) and to treat warts, keratoses and other hyperplastic skin diseases. Escharotics have also been used to seal cutaneous ulcers and wounds.

Examples: (1) Silver nitrate, phenol and antimony trichloride – frequently used for removal of warts.

(2) Glacial acetic acid – occasionally used for removal of warts.

(3) Antimony trichloride – The compound has been used as an ingredient of debudding preparations for calves. It is usually combined with salicylic acid to soften the keratin layers of the skin in concentrations of about 28% chloride (antimony trichloride) with 5 – 7% acid.

Points to ponder while debudding:

- The caustic debudding preparation does not adhere to wet or greasy surfaces. It is therefore necessary, before applying the collodion, to clip, clean and de-fat the horn bud area with ether or chloroform.
- Normal skin surrounding the skin bud should be protected by the application of a protective greasy ointment such as zinc oxide ointment.
- Debudding, to achieve the best results should be carried out within 48 hours of birth, and treatment should be thorough.

SKIN DISINFECTANTS:

Removal or reduction in bacteria on the skin by disinfectants is a useful part on the treatment of pyodermas. The agents used include those used for skin disinfection prior to surgery (e.g. povidone iodine, chlorhexidine, cetrimide and hexachlorophene) and also specific skin disinfectants, particularly benzoyl peroxide.

Benzoyl peroxide: It slowly releases oxygen and this is bactericidal, esp. towards anaerobic or micro-aerobic bacteria. The compound is also keratolytic and antiseborrheic, and so, is well suited to the treatment of pyodermas. In veterinary practice, shampoos containing 2% or 5% of benzoyl peroxide are available.

(**NB:** Pyoderma of the lip fold is a common cause of bad breath in dogs and this responds well to bathing with benzoyl peroxide).

ANTIBIOTICS AND ANTIBACTERIALS:

Antibiotic therapy is often a necessary part of treatment of pyoderma. This may be local, topical treatment in case of limited scope. More commonly the extent of the lesions requires systemic therapy. The choice of antibiotics for local treatment includes creams containing neomycin, mupirocin or fusidic acid. For systemic therapy, activity against β-lactamase producing staphylococci is important. Thus, cephalexin, clavulanate-potentiated amoxicillin and lincomycin have all been found to be effective. Treatment needs to be prolonged (in most cases more than two weeks) and relapse is rather common.

CORTICOSTEROIDS:

Examples: Hydrocortisone, Prednisolone, Prednisone, Methylprednisolone, Flumethasone, Dexamethasone, Betamethasone etc.

- ☞ Corticosteroids are used extensively to treat skin diseases in animals. These may be used topically and here the main indication is in the treatment of otitis (but it is important that a suitable antibiotic is included).
- ☞ Glucocorticoids are indicated for the treatment of many allergic dermatoses, notably allergies (flea bite dermatitis, food allergies), contact dermatitis, autoimmune diseases, pyotraumatic dermatitis ("hot-spots") etc.
- ☞ Glucocorticoids are inflammatory modulators; work better in combination with antibiotics or antifungal agents.
- ☞ Glucocorticoids have functions other than controlling inflammation and inducing immunosuppresion. Many skin diseases have neutrophil infiltration in the dermis and/ or epidermis. Glucocorticoids have a marked ability to stabilize lysosomal membranes within neutrophils, thereby inhibiting the release of enzymes that results in dermatitis.
- ☞ Since Glucocorticoids have effects on other body systems when being used to treat skin diseases, some precautionary general guidelines should be followed:--
  - (i) Be sure of the diagnosis: Glucocorticoids are generally used to relieve the symptoms of pruritis. It is important to make effort to determine it. Not performing the routine measures to determine the underlying cause of pruritis may lead to serious systemic side effects.
  - (ii) Use the least amount of steroid to achieve the clinical effect.
  - (iii) Use the least potent steroid to achieve the clinical effect.
  - (iv) Choose the route of steroid administration according to the type and severity of the lesion being treated.
- ☞ If used with suitable precautions, corticosteroids remain very valuable in treatment of otherwise intractable (unmanageable) skin conditions.

CLASSES OF MEDICATED APPLICATIONS:

Pharmaceuticals can be classified by the type of base they are formulated in. There are eight classes of medicated applications:--

(1) Ointment: It is a semi-solid preparation that usually (but not always) contains drugs used to treat dermatologic diseases.

(2) Poultice (or Cataplasma): A poultice (or cataplasma) is a soft moist mass of materials applied locally to an affected area and was historically composed of roots, herbs, seeds and even mud in a gruel like base. The poultice was intended to be a topical wound treatment serving as a counterirritant and absorptive/ adsorptive sink. Poultices are used externally as a hot or cold local application with the aim of reducing inflammation and relieving pain. Poultices are rarely used in veterinary medicine today.

(3) Pastes: Pastes are absorptive powders placed in a gelatinous base, usually petrolatum or hydrophilic petrolatum. Pastes have been used to adhere to the skin and thereby act as a sponge to absorb exudates & moisture and also as a barrier to protect the skin from the external environment. Pastes are easily removed from the skin and can be used on moist lesions of the skin.

(4) Powders: Powders are a class of vehicles used for the delivery of topical drugs to the skin. Powders are commonly used in veterinary medicine to deliver pesticides (carbaryl, permethrins etc.) for the control of external parasites (mainly fleas) and in large animal veterinary dermatology to deliver antibiotics such as nitrofurazone to wounds.

(5) Dressings: Dressings are external applications of some compounds (like petrolatum, ointments etc.) on an application device such as wrap or sterile gauze and are placed over wound sites to protect the skin lesion from external environmental trauma. Dressings may also contain antimicrobial agents, such as nitrofurazone.

(6) Plasters: Plasters are similar to dressings; however, they are attached to the skin via some adhesive material. They protect skin lesions from the external environment and provide an occlusive environment. Plasters have limited use in veterinary medicine today.

(7) Suspensions: A suspension is a two-phase system composed of a finely divided solid that is dispersed in a liquid usually water. Suspensions are not utilized to any great degree in veterinary dermatology today. They are more commonly used in oral drug preparation schemes. The most common type suspension currently used topically is captan which is used to treat some types of superficial fungal infections and which also has some limited bacteriostatic properties.

(8) Lotions: Lotions are powders dissolved in a liquid, usually water or an alcohol. Lotions, like powders, tend to be cooling, drying, and somewhat mildly antipruritic. Lotions have limited applications in veterinary medicine but are used extensively in human over the counter skin-care products.

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