Pharmacology
for
veterinary medicine students

Part II
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Drugs affecting metabolism

Fluids, electrolytes and acid-base therapy

About 60 % of a normal animal's body weight is composed of water, fat, age, obese and older animals tend to have a small percentage of water of this 60 %, 33 % is within the body cells and is referred to as intracellular fluid compartment (ICF). The remaining 27 % is outside (between) the cells and is referred to as the extracellular fluid compartment (ECF). ECF may be further divided into sub-compartments (plasma 5 %, interstitial fluid 8 %, transcellular fluid 2 %, dense connective tissue and bone 12 %). Sodium is principally responsible for ECF osmolality. Osmolality in the ICF is principally determined by potassium, magnesium, phosphates and proteins. Na-K ATPase that is present in most cellular membranes (except for most canine and feline red blood cell membranes) maintains a very low intracellular Na concentration. Hence, if Na is added to the ECF it stays there and increases the osmolality and tonicity consequently, water is be drawn out of the ICF and into the ECF compartments until the osmolalities of the two fluid compartments are nearly equal. Chloride atoms usually follow Na atoms in order to maintain electroneurality. Glucose has a major contribution to plasma tonicity. It does not enter the cell rapidly in the absence of insulin. Albumin is important for distribution of water within the ECF. It is contributes most tonicity at the level of the capillary. In the capillaries, Na and glucose can pass freely into the lymph while, albumin is retained in the vessels, where it exert a tonic force, drawing fluid back into the capillary.

Body water turnover:

1-regulated by thirsty and drinking control centers and ADH, responding to osmolarity changes

2-50-130 ml/kg/day. 65 mg/kg/day in mature animals

3-The role of skin and body surface

Sodium: Sodium intake normally occurs when an animal eats or drinks, animal receiving medications may have substantial Na intake via drugs. Under normal conditions, the kidneys regulate Na from the body.

Potassium: Regulation of total body pot. and plasma pot. concentration is important because pot. has a major influence on resting cellular membrane potentials. Hypokalemia lowers the resting membrane potentials and subsequent contraction of the muscle, hypokalemia raises the resting membrane potential, which may result in a diminished action potential amplitude or in extreme cases, continuous depolarization of the cell membrane. Internal pot. balance refers to the distribution of the pot. into the ICF and ECF compartments. The Na-K Atpase found in cellular membranes actively transport pot. into the cell and maintains a high intracellular concentration. Insulin and epinephrine augment the transport of pot. into the cells.

Role of the kidney in water and salt regulation:

1- 80-90% of water, Na, etc is reabsorbed bed from the proximal tubule.

2-Role of the loop of Henle, distal tubule & countercurrent mechanisms.

3-Role of the ADH and aldosterone.

Acid-Base Status

The body must deal with very large amounts of (H^+). The pH of 7.40 is a normal blood pH. There are two categories of acid found in the body non volatile produced by metabolism especially for proteins and ammonium in the liver and volatile, CO_2 produced by cellular respiration throughout the body. Non volatile acid excreted by the kidneys whereas volatile acid CO_2 excreted by the lungs. The principle buffer in the ECF is the bicarbonate-carbonic acid system which only reacts with non volatile acid. Ca. carbonate and Ca. phosphate in bone have a major buffering capacity, whereas intracellular phosphates and proteins are important for both volatile and non volatile acids. Volatile acid (CO_2) is not buffered by the bicarbonate system . It is buffered by proteins. When there is excessive nonvolatile acid present, it reacts with the bicarbonate buffer system. The plasma bicarbonate concentration decreases as the bicarbonate combines with H^+ and forms H_2CO_3. The result is that the HCO_3-PCO_2 ratio decreases meaning that the pH is less and there is academia (too much acid in the blood). This is called metabolic acidosis because it has a disorder causing excessive non volatile hyperventilation, this is a normal compensatory response.

N.B:- Buffer systems:

a-Intrinsic buffering system: bicarbonate, phophorus, protein, organic substances. b-K^+-H^+ pair. c-Respiratory and renal components.

Acid-base parameters and terminology:

1-At pH 7.4 the ratio of HCO_3-/H_2CO_3=20/1

2-Determination of the whole-blood buffer base using the siggoard-Anderson monogram. Base deficit/excess is defined as the titrable acid or base, respectively, when titrating to pH of 7.4 under standard conditions of PCO_2 (40 mm hg) temp. (38 ^oC) and complete hemoglobin oxygenation.

3-Acidosis & alkalosis.

4-Anion gap : The difference between the concentration of Na^+(140 mEq) and the sum of the concentrations of HCO_3-(25 mEq) and Cl-(105).A normal range is 8-12. Anion gap is contributed by metabolic acidosis.

General concepts of the fluid therapy

I-Institution of therapy

1-Causes dehydration and over hydration.

2-Role of electrolytes on hydration states and acid-base balance.

3-Role of carbohydrate and protein metabolism.

4-Clinical examination and diagnosis, blood and urine analysis are important e.g. urine pH, PCO2, HCO-.

Fluids to be used in acid-base disturbances

1-Metabolic acidosis:

a-Causes: severe diarrhea, excessive salivation, ketosis, severe tissue break-down, renal insufficiency, dehydration, hyperkalemia, chemical poisoning.

b-Signs: hyperpnea, CNS depression

c-Laboratory data and pathogenesis: ↑ H^+ & ↓ HCO_3

d-Therapy: $NaHCO_3$, Na lactate, lactated Ringers, Na gluconate, Na acetate

2-Metabolic alkalosis:

a-Causes: vomiting, gain of base, GI stasis, loss of K^+ and H^+

b-Signs: hypopnea, CNS stimulation

c-Laboratory data: ↓ H^+ & ↑ HCO_3

d-Therapy: treat etiology, NH_4Cl in NaCl, methionine, ascorbic acid, vinegar, Ringers.

3-Respiratory acidosis :

a-Causes: respiratory distress, CNS poisoning

b-Signs: respiratory distress, CNS depression, cyanosis, ↑ catecholamine release.

c-Laboratory data: ↑ H^+, PCO_2 (> 45 mm Hg)

d-Therapy: proper ventilation, others same as in metabolic acidosis

4-Respiratory alkalosis:

a-Causes: over heat, hyperventilation, encephalitis, CNS stimulant, salicylate poisoning

b-Signs: hyperpnea, CNS stimulation

c-Laboratory data: ↓ H^+, ↓ PCO_2 (< 35 mm Hg)

d-Therapy: CO_2 ventillation, sedation, others same as in metabolic alkalosis

Amount of fluid to use:

1-Must be based on the body water maintenance plus replacement of deficit and ongoing loss

2-Administration guide lines: 4, 6, 8, 12 % of the body weight. Only loss 4 % needs replacement

3-Relationship between the maintenance of the body water (65 ml/kg/24 h) and calories is about 3/4 ml/kcal/day; for dogs and cats

4-Additional circumstances need to be considered

a-Dehydration affects young animals much faster

b-Old patients with chronic diseases require more water

c-Physical and weather condition d-Drugs will alter requirements

Rate of infusion:

1-If the heart, kidney, lungs normal, the maximal rate of administration is 90 ml/kg/hr for isotonic solution in small animals and 20 ml/kg/hr in large animals

2-Rapid administration of glucose leads to glucosuria

3-Rate of infusion should be showed down after 1st hour of administration especially if no urine flow. 4-Watch for adverse reactions

Transfusions

1-Major indications for whole blood therapy :

a-hemorrhage or shock (note: normal blood volume is 75 ml/kg)

b-anemia c-coagulation abnormalities d-provision of antibodies

2-Administration and dosage

a-rate of administration depends on sign and dose b-10-20 ml/kg

3-Interspecies transfusion is prohibited

4-Plasma expanders : plasma and dextran

Restoring blood volume

1-Plasma expanders, whole blood as 10 ml/min and blood plasma 40 ml/kg

2-Plasma substitutes : dextran, 6 % solution and saline I/V

3-Parentral feeding by: glucose 10 %, 5 % nitrogen with or without glucose 5 %, Fats (cotton seed oil 15 % with glucose 4 % as emulsion I/V with electrolytes).

Properties of plasma substitutes

1-The viscosity and pH as blood 2-Osmotic pressure as plasma protein

3-Stable at different rate of temperature 4-Easily to be sterilized

5-Non toxic 6-Lopng duration of action in circulation till the plasma is restored

7-Complete excretion or metabolized

Special problems in fluid therapy

A-In horse:

1-In cases of severe diarrhea, shock or GI obstruction may predispose to severe metabolic acidosis

2-respiratory acidosis associated with gas anesthesia

3-Svere hyponatraemia associated with dehydration

4-Svere hyperkalaemia associated with acidosis in foal

B-In cattle:

1-Metabolic alkalosis associated with abomasal disease

2-Severe metabolic acidosis associated with grain overload, calf diarrhea

3-Easy to get K^+ deficit

C-In all species:

1-Heat exhaustion and prostration :- severe losses of Na^+, K^+, Cl^- and H_2O, compensatory respiratory alkalosis

2-Burns and other surgical stresses. Metabolic alkalosis due to corticosterois release among other things

Electrolytes

Therapy for electrolyte disorder primarily consists of supplementing electrolytes or decreasing the plasma concentrations by increasing excretion or diluting or sequestering the electrolyte

N.B: In small animals, the major electrolyte disorders are hypokalemia and hyperkalemia.

Restoring water electrolyte balance as follows:

1-By giving 0.9 % (NaCl, KCl and $CaCl^2$).

Excessive $CaCl^2$ leads to toxicity or

2-Administration of glucose solution 10 %

3-administration of Na lactate

II-Adrenocortical hormones (Mineralocorticoids)

They regulate the water and electrolytes metabolism

1-Aldosteron secretion is affected by Na, K in the plasma and kidney rennin, ACTH from pit. gland and glomerulotropin (pineal area)

*Absence of aldosteron leads to :

i-losses of large amounts of NaCl and water

ii-reabsorption of K by the kidney tubules
iii-imbalance of Na/K in the tissues
iv-haemoconcentration, fall in blood pressue and metabolism due to water loss

2-Deoxycortone acetate

Source….synthetic hormone. Similar but weaker than aldosteron

3-Fludrocortisone…Source….synthetic hormone.

III-The Antidiuretic hormone (ADH)

Source: secreted from posterior pituitary gland

Mode of action: ADH regulate the excretion of water by action on the renal tubules stimulating water reabsorption

Absence of ADH leads to that collecting tubules are impermeable to water hence a large volume of diluted urine is produced

Therapeutic use: In case of diabetis insipidus

IV-Diuretics

Definition…diuretics are the drugs which increase the rate of excretion of NaCl and water from the kidneys

Therapeutic uses: 1-reduce excessive water in case of edema
2-removal of toxic substances from the body
3-pH of the urine and elimination of certain drugs

Drugs affecting inorganic metabolism (Disturbances in Na, K, Ca and Mag. Metabolism) leads to certain diseases

Sodium (Na+)

*Sodium (Na^+) is the main cation in the extracellular flui

***Distribution:** 1-bone 47 % 2-extracellular 53 %

***Excretion :** saliva, sweat, urine and GIT

***Action of the Na**

1-regulate O.P 2-increase cell permeability

*Na^+ excess by excessive parentral saline solution, while, Na^+ deficiency caused in diarrhea, vomiting and low intake of Na with diuretics

Potassium (K^+)

Ph. K. of K^+:

*Absorption…. K^+ absorbed from ileum

*Metabolism… K^+ metabolism is controlled by aldosteron H

*Distribution….2 % extracelluar, 95 % intracellular, 3 % in the skeletal muscle

Actions of (K^+)

1-estabishment of the membrane potential of the cells
2-depolarization conduction of impulses followed by depression of the tissue
3-depress the heart rate
4-presence of K^+ and Ca^+ help in the contraction of muscles
5-K^+ not excreted in case of kidney damage leads to death

Causes of K^+ deficiency:

1-starvation and injury 2-certain diuretics as thiazides 3-in case of diabetis (increase inside the cell, glucose, insulin and K^+….leads to hypokalemia 4-digitalis increase K^+ loss 5-less of carbonates or chloride…leads to deficiency of K^+ 6-aldosteron high level, ACTH and Na salts increases K^+ excretion

K^+ excess:

Over dosage of K^+ or tissue injury by trauma results in cardiac arrhythmia

Treatment of K^+ excess:

1-Na^+ polystyrene sulphonate which exchange Na with K ions

2-Ca borogluconate

Therapeutic uses:

As diuretics for horses and cows.

Give pot. citrate, pot. acetate and pot. chloride

Calcium

Calcium distribution in the body

-Ca constitute about 20 % of b.wt. -Plasma Ca^{++} 10 mg/100 ml

Pharmacokinetics:

*Absorption: Ca^{++} slowly absorbed in the first part of small intestine and its absorption is reduced in alkaline media. But the absorption is increased in the presence of vit. D and protein high diet

*Metabolism:

-After absorption Ca^{++} reach bone in the presence of vit. D., parathyroid hormone and thyroxine. So the factors affecting Ca^{++} metabolism are:-

1-parathyroid hormone which is responsible for maintaining normal blood Ca^{++}

2-steroidal hormones……..oestrogen and androgen…..retain Ca^{++}

ACH……..decrease Ca^{++} level

3-Thyrocalcitonin, which decrease Ca^{++} level in the body by

a-inhibit Ca^{++} resorption from bones

b-antagonize the effect of parathyroid hormone

4-Vit. D……..D2 (needs bile for absorption), D3

-Vit. D is used for the treatment of rickets given in the form of cod liver

-Calciferol or vit. D3 given by injections for dogs and cats

*Excretion: the excretion of Ca^{++} occurs mainl via gut

-the following % in different animals, the excretion of Ca^{++} occurs :

I-ruminants		II-horses		III-dogs
10 % (in urine)	90 % (in feaces)	50 % (in urine)	50 % (in feaces)	via gut only

***Pharmacodynamics:**

Pharmacological actions:

1-in the presence of excess of Ca^{++}, the cell membrane permeability is decreased to Na^+ and K^+

2-Ca^{++} is connecting with the stimulation for the secretion of ADH and catecholamine

3-Ca^{++} is necessary for the Na^+ pump mechanism to extrude Na^+ after depolarization

4-The lack of Ca^{++} in the body leads to :

a-increased muscle irritability which leads to titanic spasms by increasing cell permeability for entry of Na^+ in the cell

b-decrease the amount of Ach, consequently decrease of release of adrenaline

5-When Ca^{++}, increased its level above 12 mg/100 ml of the blood leads to :
a-muscle weakness b-decrease the activity of the smooth muscles resulted in constipation, indigestion and loss of appetite c-in the presence of vit. D, Ca^{++} excess may deposited in the vital organs as heart or the kidney

Therapeutic uses of Ca^{++}: Ca^{++} is used therapeutically in the following:
1-milk fever in cows in the form of ca. borogluconate and Ca. levlinate
2-vit. D deficiency 3-pregnancy 4-rapid growth
5-certain poisons as carbon tetrachloride 6-prolonged deprivation of Ca

MG^{++}

Pharmacokinetics:

*Absorption : the presence of parathyroid hormone stimulate absorption of MG^{++} from the gut. Whereas presence of MG^{++} in high concentration in the blood reduce the secretion of parathyroid hormone
*Distribution of MG^{++} after absorption intracellular and about 2/3 in the bone. The concentration in the fluids (2-4 mg/100 ml).
*Excretion of MG^{++} occurs in urine, where in ruminants occurs in the gut

Ph. Actions of MG^{++}

1-it inhibit the release of Ach at the neuromuscular junctions
2-it increase the Ach synthesis by increasing the synthesis of choline acetylase
3-it maintain the contraction of smooth muscles
4-it activate ATPase and adenyle cyclase enzymes
5-it depress the CNS and respiratory centers

Therapeutic uses of MG^{++}

1-MG^{++} sulphate 25 % + chloral hydrate + Ca borogluconate S/C used as general anesthesia and skeletal muscle relaxant 2-MG^{++} sulphate solution 25 % S/C used in the treatment of hypomagnesaemia 3-MG^{++} sulphate used as purgative and antacid 4-MG^{++} sulphate,I/V destroy stray dogs

Phosphorus

Ph. Actions:

1-inside the cell phosphorus is used in the energy transfer as it was found in nucleic acid. 2-it is used as tribasic calcium phosphate and phosphoric acid in case of hypophosphataemia 3-it is a buffer system to adjust body pH

Manganese (Mn)

It is an essential for life and is trace element. It is rapidly absorbed and fixed in the liver then slowly excreted in the urine and bile. Lack of Mn in chickens leads to slipped tendon which leads to osteoporosis of bones

Drugs affecting tissue metabolism

I-Thyroxine + Liothyronine

Source: From amino acid tyrosine + iodine (thyroglobulin) $\rightarrow$ Thyroxine

Ph. Actions:

1-They increase tissue metabolism (all tissues) increasing O_2 consumption, CO_2 production and body temperature
2-On the heart : they increase the excitability of sympathetic receptors leading to increased pulse rate and rhythm
3-On (pancreas and liver): They increase blood sugar and decrease the liver glycogen

4-They increase the urinary excretion of Ca^{++}, Na^{+} and water

II-Iodinated proteins

Composition I, Casein, Egg albumin and Soya bean protein

Ph. Actions: similar to thyroxine

Therapeutic uses (Thyroxine and Iodinated proteins):

1-stimulation of milk production 2-improve fertility in bulls 3-↑ growth rate in young animals 4-preventing decline in egg laying due to age or in summer

Dose: 2.5 mg/kg for large animals

III-Anti-thyroid drugs

e.g….1-sulphonamides (sulphaguanidine) 2-thiamides (thiourea and thiouracil)

Action: They caused ↑ in the body weight and hyperplasia of thyroid gland

Mode of action: Act by interfering with the combination of iodine and tyrosine

Therapeutic uses: ↑ body gain in chickens 2-depress egg laying and milk production

Dose: 1-4 gm for large animals and 1 % to feed in poultry

IV-Vitamin A

Source: cod liver oil and halibut

Actions: 1-necessary for tissue metabolism
2-maintainingh epithelial surface
3-improved in the synthesis of glucocorticoids.

Vit. A toxicity:

1-Premature closure of epiphysis. 2-fractures. 3-anorexia.

Treatment of vit. A toxicity: By administration of vit. K.

V- Vitamin D

Source: Plant, animal and synthetic. The synthetic vit. D are calciferol (vit. D_2) and cholecalciferol vit. D_3).

Actions: 1-antirachitic activity. 2-act to mobilize Ca^{++}& PO_4^{++} from bone.
3-it maintain the circulating level of Ca^{++} in the blood together with parathormone.

VI- Vit. E

Source: Plant (wheat germ oil) and synthetic form (tocopherol acetate) I/M.

Actions:

1-it prevent certain metabolites that form toxic oxide.
2-it prevent the formation of an oxidation-reduction potential in cartain tissues.
3-it act as prothetic gp. in some enzymes.
4-it play an important role for normal reproductive processes.

VII-Factor 3 (selenium)

It present in the liver. Its effect as vit. E.

VIII-Vitamin B complex

Def. They are group of vitamins which is necessary for normal tissue metabolism. They include the following:

Vit. B_1 (Aneurine, thiamine): This vitamin is known as Aneurine diphosphate is the co-enzyme which enables the carboxylase enzyme to oxidize pyruvic acid. Dose-----Aneurine chloride 1-10 mg

IX-Vit. B2 (Riboflavin)

Action: Riboflavin phosphate combines with a protein to form the yellow co-enzyme which is concerned with the cell respiration. Dose---2-10 mg.

X-Nicotinic acid (nicotinamide, niacin)

Source: Tryptophan---------- niacin---------store in liver

Action: Niacin forms a part of co- hydrogenase concerned with the tissue oxidation, especially dehydrogenation of glucose to triose phosphate.

XI-Vit. B6(Pyridoxine)

Action: It is co-enzyme concerned with protein metabolism. Dose :125mg

XII-Biotin

Concerned with the growth

XIII-Folic acid (petroylglutamic acid)

Source : Green leaves. It is essential for growth

Action : Folic acid is reduced by enzymes to tetrahydrofolic acid which acts as an acceptor of certain one carbon unit involved in purine and pyrimidine nucleotide biosynthesis and inter conversion of some aminoacids.

XIV-Vit. B12 (Cobalamines)

It contains vit. B_{12a} (hydroxycobalamine) and vit. B_{12b} aquacobalamine.

Source :1-liver 2-products of metabolism of certain microorganism

Functions : 1-Metabolism of CHO& fat & protein.

2-Essential for the growth and laying eggs.

3-Prevent liver damage by affecting transmethylation.

4-It is essential for nucleoprotein synthesis.

XV-Vit. K

Source :1-bacteria of large intestine synthesize the vit.

2-Plant origin phytomenadione (vit. K) given I/M and orally.

3-synthetic vit. K (Menaphthone sod. Bisulphite vit. K analogue----given 5 mg I/M).

Action: Vit. K is essential for the liver to make prothrombin and other collecting factors. Dose :----50-60mg.

Iron(Fe+++)

Therapeutic uses:

1-treating iron deficiency anemia by using---ferrous sulphate orally for horses and cattle and scaly preparations for small animals as iron ammonium citrate.

Preparation :

-iron pyrophosphate (capsules or pastes)

-iron dextran (I/M), Ferrivenin (I/V).

2-As haemostatic or styptic----as ferric chloride used externally.

3-Astringent as ferrous salts given orally for diarrhea.

Copper

Therapeutic uses :

1-calcium copper edentate---used in case of copper deficiency.

2-copper sulphate---1 % and 10 %

*copper sulphate 1 % in case of :

a-close the oesophageal groove in ruminants b-emetics in case of dogs.

c-astringent for diarrhea. d-eye in conjunctival irritation.

*copper sulphate 10 % :

a-as antiseptic as in case of F & M disease b-fungicidal. c-molluscicidal.

Cobalt

Source: 1-cobalt bullet in the rumen orally. 2-cobalamine inj.

Ph. K.----Rapid absorption from intestine. Excretion through bile and kidney.

Drugs affecting CHO metabolism

Disturbance in CHO metabolism, leads to ketosis in cattle, hypoglycaemia in piglets and diabetis in dogs. Drugs which are used in the treatment of such disturbance are all vit. And hormones such (thyroid, adrenaline, glucagons and insulin).

Glucagon

Source:--------(Biological) ---- α cells of pancreas

Action and mode of action :

*it increases the blood sugar by activating the liver phosphorylase and so increasing glycogenolysis. *It increases gluconeogensis as corticoids.

Insulin

Source:---B cells of islets of pancreas

It consists of polypeptide containing cystine residues.

Therapeutic uses :----It is useful in case of diabetis in dogs.

Dose :----5-50 units S/C.

Synthetic hypoglycaemic agents

1-Sulphonyl-urea group

Action and mode of action :

It produced a marked hypoglycaemia by stimulating the secretion of insulin from pancreas. It is given orally, it have no toxic action on bone marrow and have no antibacterial action.

a-Tolbutamide (Rastinon)---metabolized in liver into inactive form and excreted in urine.

b-Chlorpropamide (Diabenase)----

2-The Biguanides

Mode of action :

It is a new oral antidiabetis acting by augmenting the action of insulin.

Action : After 2 hours of oral administration induce hypoglycaemic effect lasting for 6-12 hours. e.g……. a-Metaformin (Glucophage) b-Phenformin

Glucogenic agents

These are drugs that stimulate the formation of glucose from proteins and increasing the glucose level in the blood.

1-The Glucocorticoids are drugs used in the treatment of ketosis in dairy cows

2-Propylene glycol 3-Sodium propionate

These drugs for treating of ketosis in cattle & pregnant toxaemia in sheep

Growth promoters

and production in animals producing food for human consumption

Objectives :

1-To increase rate of gain 2-Toincrease feed efficiency.

3-Toincrease ratio of protein (lean) to fat in meat.

4-Toprevent and / or reduce the effects of disease.

Different means that may by used :

1-Genetic selection of animals.

2-Ration formulation to balance the diet and to provide for stress.
a-vitamin, minerals, energy, protein.
b-rumen by-pass nutrients such as protein and fat.
3-Antimicrobial drugs. Usually used as feed additives: sulphonamides, antibiotics, arsenicals.
4-Antiparasitic. drugs. a-to control internal and external parasites.
b-feed through fly larvicides for control.
5-Ionophore antibiotics : monensin, lasalocid, salinomycin
6-Hormonal activity drugs a-estrogen, androgen, progestin implants.
b-growth hormone.
7-probiotics. 8-Repartitioning agents. 9-Good management practies.

Feed additives

Ionophores

1-They are carboxylic polyether ionophore antibiotics
e.g. Monensin, lasalocid and salinomycin.
1-monensin used for poultry, beef cattle and goats.
2-lasalocid used for poultry, cattle and sheep.
3-salinomycin used for poultry for control of coccidiosis.

Monensin and lasalocid are labeled for cattle to ↑ weight gain and feed efficiency. Also labeled for sheep and goats and poultry to control coccidia.

II-The ionophores all have antimicrobial action against certain bacteria and protizoa.
a-they have very selective action against only certain of the rumen microflora.
b-they are not effective against animal pathogens

Mode of action of ionophores:

1-they alter membrane transport and cellular metabolism of both bacterial and mammalian cells. They change the flux of Na/K and also Ca.
2-this is harmful to certain M.O. in the rumen, affects mainly gram positive bacteria. Does not affect others. This reduces certain populations and others fill the void. This then changes the rumen microflora.

Desired action of ionophores (cattle) :

1-increased weight gains by increasing feed efficiency.
2-reduced incidence and severity of bloat.
3-reduced incidence and severity of high concentrates (overload) lactic acidosis and rumenitis.
4-are effective coccidiostats.
5-prevent/reduce tryptophan induced pulmonary edema and emphysema.
6-usual recommended daily intake
Rumcnsin (moncnsin) 0.5-1.1mg/kg/day P.O. Bovatec (lasalocid) 1-1.5

Adverse effects (side effects) :-

1-may affect mammalian cells, that have high membrane transport (e.g. kidney and liver), also those cells in which Ca is involved in muscle contraction such as heart and muscle.
2-horses are more susceptible than cattle due to horses have greater absorption from the gut and the plasma elimination half times are different cattle elimination half time = one hour

horse " " " = 8 hours.

So greater absorption and slower elimination will give the horse higher plasma and tissue level.

LD_{50} for monensin :

cattle----20-40mg/kg, horse---2-3mg/kg, swine---7mg/kg, sheep---8-12mg/kg

LD50 for lasalocid :

Ld50 for cattle---50mg/kg., Horse 22mg/kg, Swine 58mg/kg

Implants---Cattle

They are 1-Estradiol-----each dose contains 24mg estradiol

2-Progesterone+estradlol

Implants in cattle

1-Synovex II (Testosterone and estadiol)

100 day response time, no slaughter withdrawal time. Each dose contains 20 mg of estradiol benzoate plus 200mg of testosterone propionate.

2-Synovex C (progesterone + estradiol)

100 day response time, no withdrawal time. Each dose contains 10mg of estradiol penzoate + 100mg progesterone.

3-Zeranol :--synthetic estrogen

100day response time, no withdrawal time. Dose contains 36 mg for cattle 3 pellets and sheep one pellet (12 mg)

4-Trenobolone acetate :

is a testosterone like anabolic dissolving pellets

dose 140-200 mg

Actions - All are anabolic

They induce the following : 1-increase in the weight gain

2-deposit more protein in the animal body

3- " less fat " " " "

Mechanisms for their anabolic action :

1-Estradiol :

a-increase plasma growth hormone which in turn increases muscle and bone synthesis

b-increases plasma insulin which increases glucose and aminoacid uptake by the cell. This favors increased protein synthesis

c-increases plasma thyroxine which increases growth

2-Progesterone : anabolic, similar to estradiol

3-Testosterone :

a-have a direct anabolic action on muscle cells

b-reduces muscle cell cortisol, which leads to less protein catabolism

N.B.: FDA has declared the use of implants safe. A safe level of added hormone is stated as being less than 1 % of the amount the human body produces. e.g…a person could safely eat 4,000 pounds of beef each day

Probiotics

Definition: is a group of products are also called fed microbials

A-Are for oral administration of live, non pathogenic bacteria and fungi

1-some are combination of bacteria, molds or yeasts

2-are intended to have their action in the intestinal tract
3-some may also add nutrients

Factors necessary for probiotic effect :

1-M.O. must be active 2-must be normal bacteria of GIT
3-need to colonize in the intestine 4-have a short generation time
5-must produce lactic acid
6-may produce substances that are antibacterial for pathogens

M.O. that are used:

1-Bacteria: streptococcus faecium, lactis and thermophilus, lactobacillus acidophilus, lactis, bacillus subtilis and toyol

2-Fungi:-live yeast -sacchromyces cerevisiae -toprulopsis -aspregillus oryzac

Objectives of probiotic therapy:

1-to maintain a proper balance in favor of beneficial microflora in the intestinal tract to hold in check the potentially pathogenic microflora
2-since it is believed that stress is a major cause of reduction in the protective microflora and an imbalance that favors the pathogens, probiotics may be indicated in stressed animals

Mode of action of probiotics:

1-production of lactic acid, lowers the pH of the intestinal contents which is unfavorable to pathogens may be more effective in neonates
2-competitive antagonism, compete with pathogens for attachment, adhesion or colonization of GIT. Which is an important aspect of an organism attempting to associate in a particular area of the gut
3-enteric flora alterations. Benificial M.O. inoculated into newborn animals prior to the establishment of a more non beneficial microflora may help the animal establish a positive microflora, aiding in the exclusion of or control of potential pathogens
4-production of antibiotics may help control pathogens
5-production of H_2O_2: H_2O_2 is detrimental to many potentially pathogen M.O.
6-production of enzymes: the non-specific effects frequently seen with probiotics may be due to the digestive enzymes which the M.O. produce
e.g….lactobacillus produce lactose
7-production of B-vitamins: the probiotic M.O. are known to be the producers of several B-vit. As metabolites within the intestinal tract
8-prevention of the production of toxic amines and ammonia
9-non-specific immunomodulators. Recent evidence in baby pigs suggest that lactobacilli may act in some manner as an immunomodulator stimulating some type of local immune response in the gut

Growth hormone (Somatotropin)

-It is a large polypeptide hormone. It contains 190-199 amino acids that differs from species to another. Bovine somatotropine is inactive in people

Treatment objectives:

Increasing the protein and decrease fat in carcass

Mode of action:

It has direct action on cell membrane and enhance the formation and secretion of insulin-like growth factor call somatomedin (IGF-1) by the liver and muscle and possibly other organs

Actions:

Increase lipolysis and stimulates hypertrophy of the muscle cells

Antimicrobials

1-Antibiotics:

Bacitracin, oleandomycin and flavomycin are antibiotics permitted only for use in growth promotion because the other antibiotics which of value in therapy against microorganisms, developed drug resistance when used as growth promotion.

2-Non antibiotics :

Quinoxaline, nitroverin arsenic, organic arsenic and copper salts used as growth promoters.

**Mechanism of action :

a-improving food absorption and metabolites. b-curing subclinical diseases.

**Adverse effect of antimicrobials as growth promoters :

1-problem of drug resistance. 2-drug residues. 3-arsenic & copper intoxication.

Vitamins

1-Cyanocobalamine (vit. B_{12}) :

It increase feed efficiency leading to impoving growth in case of chicken or in ruminant animals due to their needs for cobalt which is deficient in their ration. Also it increase the blood haemoglobin concentration in the presence of iron and copper salts

2-Vitamin A : Vit. A considered as growth promoter due to that it stimulate metabolism, consequently improve the growth rate

3-Vitamin D_3 : Calciferol in the presence of Ca^{++} ions improve growth rate especially bone. Antibiotics with vit. A and D_3 used in chicken and ruminant as growth promoter as they improve the growth rate

Tissue extracts

e.g…placenta, rumen, splenic and liver extracts have been used as growth promoters as they increase body weight and improve growth rate.

INTRODUCTION TO CHEMOTHERAPY

- Chemotherapy is the treatment of diseases by the use of a pure chemicals which has specific antagonistic effect on the infective microorganisms that cause the diseases

Anti-bacterials or anti-microbials:

- Are agents or drugs that used to inhibit the growth and multiplication or kill and destroy the infective microorganisms
- They includes 2 main groups: antibiotics and other antimicrobial agents

Antibiotics:

- Are agents or substances produced by a certain types of living microorganisms and used to inhibit the growth and multiplication or kill and destroy other living infective microorganisms
- Obtained from living bacteria, yeasts and moulds
- Effective against living bacteria, some fungi and some viruses

Classification of anti-microbial agents

I- According to antibacterial activity:

1- Bacteristatic:

- Only block the bacterial growth
- **Ex.** Broad spectrum antibiotics (TTCS, Chloramphenicol), sulphonamides

2- Bactericidal:

- Kill the bacterial cell
- **Ex.** Betalactam antibiotics (PCNS, CSPNS), AMGS, polypeptides

II- According to antibacterial spectrum:

- Spectrum means the range of microorganisms affected

1- Narrow antibacterial spectrum:

- In which the effect of drug is limited to small number of microorganisms
- **Ex.** Either to G+ve microorganisms (as PCNS, CSPNS) or to G-ve microorganisms (as AMGS)

2- Broad antibacterial spectrum:

- In which the effect of drug include a wide range of microorganisms including G+ve, G-ve bacteria, protozoa, viruses, fungi
- **Ex.** Broad spectrum antibiotics (TTCS, Chloramphenicol), broad spectrum PCNS (ampicillin, amoxicillin), fluoroquinolones

III- According to mechanism of action:

1- Group inhibit the bacterial cell wall synthesis:

- As betalactam antibiotics (PCNS, CSPNS), glycopeptides, bacitracin

2- Group inhibit the bacterial cell protein synthesis:

- As AMGS, broad spectrum antibiotics (TTCS, Chloramphenicol), macrolides

3- Group inhibit the cell membrane function (permeability) and/or formation:

a. Specific for bacteria as polypeptides (polymyxin B and E)
b. Specific for fungi as antifungal antibiotics (nystatin, amphotericin B, miconazole, ketoconazole)

4- Group inhibit the nucleic acid synthesis:

a. Effect on RNA: **Ex.** Rifamycin ….. Inhibit the replication of RNA by inhibiting the DNA-dependent-RNA polymerase enzyme concerned with this replication
b. Effect on DNA: **Ex.** Ciprofloxacin ….. Inhibit the replication of DNA by inhibiting the DNA gyrase enzyme (Topoisomerase II) concerned with this replication

IV- According to clinical uses:

1- Antiviral as rifamycin
2- Antifungal as ketoconazole
3- Antitubercular as streptomycin
4- Growth promoter as zinc bacitracin, TTCS

Factors determining the choice of antimicrobials

1- Diagnosis or identification of the causative organism
2- Determining the susceptibility of the causative organism to different antimicrobials to choose the most effective one

Considerations for choice of antimicrobial drugs

- Ideal drug is that one to which the organism is most sensitive and that achieve effective concentration at the site of infection without damaging the host
- Bactericidal drugs are required in certain cases: when host defenses are impaired and in serious infections in which host defenses are impaired as meningitis, endocarditis
- Bacteristatic drugs are required in other cases
- Narrow spectrum antimicrobials may be better used than broad spectrum ones because the 1st interferes less with the normal microbial flora
- The cost of the drug
- The withdrawal time of the drug if it has a residual effect in tissues or in milk of food-producing animals

Antimicrobial drug combinations

- Widely used to broaden the spectrum of activity especially in mixed infections

The following rules should be considered:

❖ Bactericidal + bactericidal drug combination:
- The result is usually synergistic effect (**Ex.** Pen. G. + Streptomycin is the most widely used bactericidal drug combination)

❖ Bacteristatic + bacteristatic drug combination:
- The result is usually additive effect (bacteristatics not act synergistically)
- A combination of bacteristatic drugs, which produce synergy, is that of sulphonamides and trimethoprim. This combination can be bactericidal under some conditions

❖ Bacteristatic + bactericidal drug combination:
- The result is usually antagonistic effect (**Ex.** PCN + TTC or chloramphenicol)
- Bactericidal agent kills only the rapidly growing, multiplying bacteria, but if the bacterial growth is prevented by bacteristatic agent, the bactericidal agent will no longer able to make its action sufficiently
- Combination of sulphonamides & PCN is an exception of this rule

Their clinical use (indications):

1. Treatment of severe, serious infections in which the host defenses are impaired and the causative organism is unknown
2. Treatment of mixed bacterial infections such as urinary tract, genital tract, respiratory tract infections, hepatic and brain abscesses, peritonitis
3. To provide synergism when use of single agent alone is not effective
   Examples:
   - PCN + streptomycin in bacterial endocarditis
   - Sulphamethoxazole + TMP in coliform meningitis
   - Ampicillin + clavulanic acid in bovine staphylococcus aureus mastitis
4. To provide broad spectrum activity in undefined infections or infections with more than one organism
5. To ↓ drug toxicity
6. To prevent occurrence of microbial resistance against drug especially in chronic infections as in treating tuberculosis (T.B.)

Their dis-advantages:

1. Increased costs
2. Some combinations increased risk of toxicity
3. May caused drug interactions
4. May caused super-infection after destroying the normal microbial flora
5. May leads to bacterial resistance

Failure of anti-microbial therapy may be due to

1. Misdiagnosis which lead to selection of unsuitable antibiotic
2. Inaccurate identification of the causative organism
3. Resistance of the causative pathogen
4. Intracellular location of the organism

ANTIBIOTICS

Beta-lactam antibiotics

- Includes one of the most important groups of antibiotics, Penicillins and cephalosporins

I- Penicillins (PCNS)

Source:

- Discovered by Alexander Flaming 1929
- Obtained from mold of penicillium notatum

- Also can prepared semi-synthetically

Chemistry:

- All PCNS derived from 6-amino penicillanic acid
- All PCNS consists of a thiazolidine ring connected to beta-lactam ring which is essential for antibacterial activity

Mode of action:

- Act only on young growing bacteria **i.e.** affecting bacteria during its growth
- Have no effect on resting, non multiplying bacteria or bacteria with well formed cell wall
- Act by inhibiting the bacterial cell wall synthesis by blocking the enzyme system involved in this synthesis (as trans-peptidase enzyme):
  - ♣ This enzyme help the formation of the peptide bonds (the cross-linking between amino acids) and thus makes the cell wall to be strong & rigid
  - ♣ Thus, the block of transpeptidase enzyme makes the cell wall to be not strong & not rigid & loss its integrity → the bacteria leak out its cellular contents and its death
  - ♣ The peptidoglycan layer in the bacterial cell wall is formed from two alternating amino sugars, namely *N*-acetylglucosamine (NAG) and *N*-acetylmuramic acid (NAM) The alternating sugars are connected by glycosidic bond
  - ♣ The cross-linking between amino acids occurs with the help of the enzyme transpeptidase and results in the bacterial cell wall to be strong and rigid

Resistance:

- Occur by certain strains of microorganisms which able to produce beta-lactamases (penicillinases) enzymes such as Staph. aureus, E. Coli, Pseudomonas aeruginosa
- These enzymes causes breakdown of beta-lactam ring and thus the PCN molecule become inactive
- The resistance produced by many G–ve bacteria is due to inability of the PCN to penetrate the cell wall of these bacteria

Antibacterial activity:

- Bactericidal
- Good susceptibility against G+ve bacteria as staphylococcus (except the penicillinase producer, Staph. aureus), streptococcus (as streptococcus agalactiae, streptococcus pyogens)

- Moderate susceptibility against heamophilus sp. (H. influenza), pasteurella sp., closteridia sp.
- Resistant bacteria as Enterobacteriacae or G–ve org. (E. Coli, pseudomonas aeruginosa), staphylococcus aureus, M. tuberculosis

Pharmacokinetics:

Route of administration:

- Most PCNS administrated by IM or SC injection
- Orally administrated PCNS destroyed by penicillinase enzyme secreted by some intestinal bacteria as E. coli and by gastric acidity for acid sensitive PCNS

Absorption:

- Rapid by IM & SC administration
- Poor by oral administration due to their destruction by penicillinase enzyme secreted by some intestinal bacteria as E. coli and by gastric acidity for acid sensitive PCNS

- Can delay by 2 methods:
  1- If injected in oily suspension
  2- If injected simultaneously with agents that block their renal tubular excretion as probenicid

Distribution:

- Cross the biological membranes including blood brain & C.S.F. barrier only in case of inflammation as meningitis

Metabolism:

- By hepatic enzymes

Excretion:

- Mainly through kidney and their renal excretion blocked by probenecid, thereby increasing their plasma concentration and prolonging their effects

  ♣ Probenecid (Probalan):
  - Is a medication that increases uric acid excretion in the urine
  - It is primarily used in treating gout and hyperuricemia
  - Also, reduce excretion of indomethacin, ketoprofen, cephalosporins, quinolones, lorazepam and acyclovir

Advantages of PCNS	Disadvantages of PCNS
• Bactericidal activity	• Active only against actively young growing bacteria
• Wide safety margin	• With slower killing rate than AMGS
• Their action not affected by blood elements or tissue products breakdown including pus	• Wide spread resistance in Staph. aureus & G-ve bacteria
	• Very limited oral use in horses due to causing GI disturbances
	• Narrow spectrum of activity

Clinical applications:

Cattle, sheep, goat, horse, swine:

- Streptococcal infections as acute throat infections, mastitis due to Str. Agalactiae
- Pneumonic Pasteurellosis caused by Pasteurella
- Closteridial diseases caused by closteridial bacteria as tetanus, gas gangrene, black leg disease, lamb dysentery
- Pyogenic infections caused by str. pyogens as burns, wounds, tooth abcess

Dogs:

- Urinary tract infections caused by sensitive microorganisms

Poultry:

- Necrotic and ulcerative enteritis and intestinal spirochetosis

Adverse effects and toxicity:

- PCNS are free of toxic effects
- The major adverse effects are hypersensitivity reactions (allergy) as fever, urticaria, itching, dermatitis, skin rashes …. Treated by anti-histaminics
- A hypersensitivity to one form of PCN makes the patient at higher risk of reaction to any other form of PCN
- Also allergic individuals are usually allergic to CSPNS
- GI disturbances especially in horses in orally administrated PCN as ampicillin (ampicillin-associated diarrhea)

Drug interactions:

PCNS are synergistic with:

- AMGS (**Ex.** Pen. G. & Streptomycin) against G+ve and G-ve bacteria (except micro-organisms that show resistance to AMGS)
- Beta-lactamase inhibitors or with drugs which inhibit the micro-organisms producing betalactamases (**Ex.** Clavulanic acid-amoxicillin and Sulbactam-ampicillin)

1- Narrow spectrum PCNS

- Are beta-lactamase sensitive

i- Soluble forms:

- Are water soluble, so rapidly absorbed from the site of injection and thus
- Of short duration of action (short half-life) and thus
- Must administrated at short intervals, every 6 h

a- Benzyl PCN (Pen. G):

- Short acting PCN, acid sensitive

b- Phenoxy PCNS (phenoxy methyl & phenoxy ethyl PCN):

- Orally active PCN, acid resistant

ii- Depot forms:

- Are water insoluble, so slowly absorbed from the site of injection and thus
- Of long duration of action (long half-life) and thus
- Must administrated at long intervals
- **Ex.** Procaine Pen. G: Is a combination of procaine & Pen. G

2- Penicillinase-resistant PCNS

- Resistant to staph. aureus penicillinase enzymes
- Thus protect the beta-lactam ring against these enzymes without affecting the antibacterial activity

Examples:

- Acid sensitive (**Ex.** Methicillin, nafcillin), acid resistant (**Ex.** Cloxacillin, dicloxacillin)

Clinical uses:

- Streptococcal and staphylococcal (especially Staph. aureus) mastitis

3- Broad spectrum PCNS

- Are beta-lactamase sensitive
- Acid resistant
- Better absorption orally
- Of broad spectrum activity like that of tetracyclines (TTCS) and chloramphenicol against G+ve and G-ve bacteria
- Effective especially against Coliformis resistant to TTCS as E. Coli, salmonella, pasteurella, pseudomonas, klebsiella, shigella
- Their activity increased by their combination with beta-lactamase inhibitors as clavulanic acid or sulbactam
- **Ex.** Ampicillin and amoxicillin

4- Anti-Pseudomonal (Extended spectrum) PCNS

- Are beta-lactamase sensitive and acid sensitive
- Of extended spectrum of activity especially against pseudomonas species
- **Ex.** Azlocillin, mezlocillin, carbenicillin, ticarcillin, piperacillin

II- Cephalosporins (CSPNS)

Source:

- Obtained from molds of cephalosporium acrimonium
- Are derivatives of 7- amino cephalosporanic acid
- Share the following properties with PCNS:
    1. Contain beta-lactam ring in their structure
    2. Are bactericidal and of the same mode of action
    3. Of short half-lives
    4. Excreted through kidneys

Advantages:

- Highly beta-lactamase resistant
- Relatively acid resistant
- Relatively non toxic and can used in many PCN-sensitive individuals
- Of broad spectrum activity against G+ve and G-ve microorganisms

Adverse effects and toxicity:

- Are one of the safest anti-microbials
- Allergic and hypersensitivity reactions as that of PCNS
- Vomiting and diarrhea with orally given CSPNS

- Allergic individuals to PCNS show cross sensitivity reactions to CSPNS

Classification:

1- Old classification

- According to antimicrobial activity, resistance to beta-lactamase, accessibility to CSF and route of administration

<table>
<tr><th>1st generation</th><th>2nd generation</th><th>3rd generation</th></tr>
<tr><td rowspan="2">Of higher activity against G+ve (including Staph. aureus) and ↓ activity against G-ve bacteria</td><td>Of wider spectrum of activity than the 1st gen.</td><td>Of wider spectrum of activity than the 1st and 2nd gen.</td></tr>
<tr><td>Of ↑ activity against G-ve bacteria including Pseudomonas aeruginosa</td><td>Of higher activity against G-ve bacteria including Pseudomonas aeruginosa</td></tr>
<tr><td>Of ↑ resistance to G+ve staphylococcal beta-lactamase</td><td colspan="2">- Of ↑ resistance to beta-lactamases of G-ve bacteria including those of Pseudomonas aeruginosa
- this ↑ in resistance is usually at expense of ↓ activity against G+ve bacteria</td></tr>
<tr><td colspan="2">Not cross CSF, thus not treat meningitis</td><td>Can cross the blood brain barrier and attain higher conc. In CSF., thus used in G-ve meningitis</td></tr>
<tr><td>Examples:
- Cephradine (oral)
-Cephapirin (injection)</td><td>- Cefaclor (oral)
-Cefamandole (injection)</td><td>- Cefixime (oral)
-Cefoperazone (injection)</td></tr>
</table>

- 4th generation group characterized by

  - ♣ Extended-spectrum agents with similar activity against G+ve organisms as first-generation cephalosporins
  - ♣ Can penetrate the outer membrane of G-ve bacteria
  - ♣ Have a greater resistance to beta-lactamases than the 3rd generation CSPNS
  - ♣ Many can cross the blood-brain barrier and are effective in meningitis
  - ♣ Also used against Pseudomonas aeruginosa
  - ♣ **Ex.** Cefquinome (Cobactan)

- 5th generation group characterized by:

  - ♣ Powerful anti-pseudomonal
  - ♣ In addition, for mecicillin-resistant staph. aureus CSPNS
  - ♣ Less susceptible to development of resistance
  - ♣ **Ex.** Ceftobiprole (Zeftera)

2- Recent classification

- According to:
  - ♣ Antimicrobial activity
  - ♣ Resistance to beta-lactamase and,
  - ♣ Pharmacological properties

Orally active CSPNS	Parentral I	Parentral II	Parentral III	Parentral IV
-Cephradine -Cefaclor	-Cefapirin	-Cefotaxime	-Cefoperazone	-Cefoxitin
-Of higher activity against G+ve (including Staph. aureus) and ↓ activity against G-ve bacteria -Pseudomonas resist		-Of ↑ activity against G-ve -Minor activity against Pseudomonas -Stable to beta-lactamases	-Of ↑ activity against G-ve -Higher activity against Pseudomonas -Stable to beta-lactamases	-Of ↑ activity against G-ve -Prominent activity against Pseudomonas -More stable to beta-lactamases

III- Beta-lactamase inhibitors

- Are agents having no antibacterial activity but show synergism when administrated in combination with other PCNS
- They inhibit the beta-lactamases enzymes and thus protect the beta-lactam antibiotics from effect of these enzymes

1- Clavulanic acid

- Synthetic compound
- Usually combined with amoxicillin (in ratio 2 : 1) and ticarcillin (in ratio 15 : 1)

Clinical applications of Clavulanic acid – amoxicillin combination:

- Cattle, sheep, goat: lower respiratory tract and skin infections
- Dog, cat: urinary tract infections
- Swine: neonatal diarrhea

Clinical applications of Clavulanic acid – ticarcillin combination:

- As above but its advantage is the greater activity of ticarcillin against pseudomonas aeruginosa

2- Sulbactam

- Synthetic compound
- Usually combined with ampicillin (sultamicillin)
- Also, can combined with cefoperazone

Classification of beta-lactamases:

Beta-lactamases group	Organism	Hydrolysed agent	Inhibition by Clavulanic acid
G+ve Penicillinases	Staph. Aureus	PCNS	+
Cephalosporinases	Pseudomonas aeruginosa	CSPNS	-
Broad spectrum beta-lactamases	Enterobacteriacae	PCNS & CSPNS	+
Carbinicillinases	E. Coli and Pseudomonas aeruginosa	PCNS & carbinicillin	+
Cloxacillinases	Enterobacteriacae	PCNS & cloxacillins	+

Aminoglycosides (AMGS)

Examples and source:

- Streptomycin (obtained from mould streptomyces griseus)
- Neomycin (obtained from mould streptomyces fradiae)
- Kanamycin (obtained from mould streptomyces kanamyceticus)
- Tobramycin (chemically modified kanamycin)
- Paromomycin (obtained from mould streptomyces rimosus)
- Apramycin (obtained from mould streptomyces tenebrans)

- Amikacin (semi-synthetic derivative of kanamycin)
- Gentamicin (one of the fermentation product of micro-monospora purpurea)

Mode of action:

- Act by binding with the bacterial 30S ribosomal subunits, inducing miss-reading of the genetic code on the mRNA, causing in-correct incorporation of amino acids into the peptide chain, leading to abnormal bacterial cell protein synthesis or inhibiting the protein synthesis

Antimicrobial activity:

- Bactericidal, narrow spectrum antibiotics
- Are weak bases and their efficacy ↑ in alkaline environment (more effective in cases of enteritis and urinary tract infections), while ↓ in acidic environment (local acidity ↑ secondary to tissue damage and bacterial destruction)
- Also presence of pus materials inactivate them, thus should removed as possible
- Active mainly against aerobic G-ve bacteria (including pseudomonas aeruginosa)
- Limited activity against many G+ve bacteria especially S. aureus & streptococci
- Some mycoplasma
- Some mycobacteria (streptomycin is the most active AMGS)
- Anerobic microorganisms are generally resistant to all AMGS
- Also some pseudomonas species are resistant

Resistance:

- Occur by certain enzymes which prevent the binding of AMGS to their receptor sites on the bacterial 30S ribosomal subunits **Ex.** phospho-transferases (phosphorylation), acetyl-transferases (acetylation)
- Cross resistance can occur between AMGS in the resistant bacteria
- Chromosomal resistance developed due to presence of many 30S ribosomal binding sites

Pharmacokinetics:

- All AMGS poorly absorbed orally, but rapidly absorbed after IM or SC injection
- Of low plasma protein binding (20-25 %)
- Cross the blood brain barrier only in case of meningitis
- No significant metabolism
- Excreted in the urine by golmerular filtration

Clinical applications:

- Coliform infections in all species and poultry (salmonellosis, colibacillosis, E. Coli diarrhea, E. Coli septicaemia, enteritis, metritis, cystitis, pasteurellosis, klebsiella pneumonia, genital tract infections)
- Staphylococcal and streptococcal infections as mastitis, skin infections, ear infections
- Urinary tract infections (urine should be alkaline)
- Mycoplasma infections in animals and poultry
- Brucella infections in ruminants (streptomycin combined with TTC)
- Leptospira infections in ruminants & swine (streptomycin combined with amoxicillin)

Adverse effects and toxicity:

- Occur due to prolonged therapy and excessive high serum concentrations, over dose, liver and kidney diseases
- AMGS accumulated in high concentrations in kidney

1- Ototoxicity:
- By damaging or destroying the vestibular and cochlear (auditory) branch or division of 8^{th} cranial nerve causing: vertigo, irreversible loss of balance, irreversible loss of hearing and deafness
- Cats are the most sensitive species to this effect

2- Nephrotoxicity:
- Characterized by: albuminurea, heamaturea, renal casts, ↓ GFR which caused ↓ excretion of AMGS and ↑ of their serum level with creatinine and urea

3- Neuromuscular blockage:
- All AMGS caused skeletal M paralysis (curare-like effect) by blocking release of Ach at the neuromuscular junction
- The risk ↑ when given concurrently in combination with drugs of curare-like effect
- This effect can treated by reversible anti-cholinesterases (as neostigmine or edrophonium) or IV injection of calcium salts (as Ca. gluconate 10 % solution)

Drug interactions:

- AMGS are synergistic with beta-lactams (PCNS) especially against enterococci (Streptococcus fecalis)

- AMGS potentiate the nephrotoxic effects of other nephrotoxic drugs such as thiazide and loop diuretics, antibiotics as amphotericin-B

Spectinomycin

- A product of streptomyces spectabilis, like AMGS in mode of action but it is not AMG
- Lacks most of the toxic effects of the AMGS (not induce ototoxicity or nephrotoxicity but may induce neuromuscular block)
- Development of resistance limit its long term use
- Bacteristatic, broad-spectrum antibiotic (can be bactericidal)
- Pharmacokinetics like that of AMGS
- Its activity against mycoplasma ↑ by its combination with lincosamides (lincomycin-spectinomycin combination)

Used mainly for:

- Mycoplasma infections
- G-ve bacterial infections (E. coli, diarrhea, septicemia)
- Salmonellosis and mycoplasma bovis in calves
- Poultry diseases (mycoplasma infection, CRD, pasteurellosis, salmonellosis, E. coli)

Broad-spectrum antibiotics

I- Tetracyclines (TTCS)

Source and examples:

- Obtained from streptomyces species

1- Short acting TTCS:
  - Chlortetracycline (obtained from streptomyces aureofaciens)
  - Oxytetracycline (obtained from streptomyces risomus)
  - Tetracycline

2- Long acting TTCS:
  - Doxycycline and minocycline

Mode of action:

- Act by binding with the bacterial 30S ribosomal subunits, thus inhibiting the incorporation of amino acids into the peptide chain, and thus inhibiting the bacterial protein synthesis

Anti-microbial activity:

- Bacteristatic, broad spectrum antibiotics
- Bactericidal at high concentrations like that attained in urine
- Effective against G+ve and many G-ve bacteria, all anaerobic bacteria, some species of mycoplasma, some species of rickettsia and some species of chlamydia
- Also, effective against some protozoa species especially entamoeba histolytia (amoebiasis)
- Minocycline has a greater activity than other TTCS against nocardia, some mycobacteria, anaerobes and some strains of staphylococcus aureus

1- Good susceptibility against:

- G+ve aerobes as: actinomyces pyogens, bacillus anthracis, corynebacterium pyogens, listeria monocytogen, many staphylococcal & streptococcal species
- G-ve aerobes as: some enterobactericae (heamophilus, pasteurella), brucella
- Some mycoplasma as: Mycoplasma gallisepticum
- Some species of chlamydia
- Some species of rickettsia
- Some protozoa species especially entamoeba histolytia, thieleria, anaplasma, babesia

2- Moderate susceptibility against:

- Leptospira species

3- Variable susceptibility (due to acquired resistance) against:

- E. Coli, salmonella, klebsiella

4- Resistant:

- Mycobacteria species, nocardia
- Acquired resistance in some enterobactericae (E. Coli, klebsiella, P. aeruginosa)

Pharmacokinetics:

- Administrated orally, IM or IV
- IM not recommended in horses due to painful reactions & local tissue damage

Absorption:

- Impaired by presence of food especially milk and its products, metal ions as Ca^{++}, Fe^{++}, Mg^{+} salts and aluminium hydroxide gels ….. all

binds with TTCS forming insoluble chelated complexes, thus ↓ their absorption and bioavailability
- Minocycline and doxycycline poorly chelate with Ca^{++}, Mg^{+} and their absorption not affected by food but chelate with Fe^{++}
- Destroyed by ruminal bacteria when given orally and interfere with normal fermentation processes

Distribution:
- Widely distributed in all body tissues and fluids except CSF
- Newer TTCS (minocycline and doxycycline) especially minocycline have greater capacity than older TTCS to attain higher concentrations in tears and prostatic fluid
- Because of their chelating properties with Ca^{++}, they tend to deposited in growing bones & teeth
- Cross the placenta and reach the fetus
- Secreted in milk and reach concentrations equal to those of serum

Metabolism:
- Limited

Excretion:
- All (except minocycline and doxycycline) excreted unchanged in urine, mainly by glomerular filtration
- Impaired renal function can ↑ their half-life
- Minocycline excreted partly by metabolism
- Doxycycline excreted by intestine in bile and feces

Drug interactions:

- Synergistic with tylosin against pasteurella
- Doxycycline synergistic with rifamycin or streptomycin for brucellosis

Resistance:

- Acquired resistance among bacteria and mycoplasma
- Cross resistance among TTCS

Adverse effects and toxicity:

- Are relatively safe drugs, of wide safety margin

- Adverse effects are due to:
  - Their severely irritant nature (vomiting orally & tissue damage parentrally)

- Their ability to bind Ca^{++} (cardiovascular effects and deposition in bone and teeth)
- Their hepatic and renal toxic effects
- Disturbance of intestinal flora

1- In humans:

- Nephrotoxicity and hepatotoxicity due to IV over dose
- **Super-infections**: by strains of resistant bacteria and yeasts leading to GI disturbances (staphylococcal enterocolitis, intestinal candidiasis, killing of vitamin B forming bacteria leading to vitamin B deficiency, thus vitamin B complex should given during treatment with TTCS in case of prolonged therapy)
- **Local irritations**: orally (irritation, vomiting), IV (swelling, necrosis, thrombophlebitis), IM (pain, swelling, necrosis)
- **Hypersensitivity reactions**: skin rashes, drug fever, dermatitis, cross sensitivity among different TTCS

2- In children:

- TTCS deposited in teeth and bones and by chelating properties bind to Ca^{++} and caused yellowish-brown discoloration of teeth and depressed bone growth (inhibit calcification)

3- In animals:

- **Cattle**: nephrotoxicity and hepatotoxicity by high IV dose
- **Horse**: inhibition of intestinal microflora and predispose to super-infection with resistant salmonella (Colitis), leading to severe or even lethal diarrhea by large IV doses or even after low IM doses, thus of limited use in horses (especially mino- and doxycycline)
- **Dogs:** fatal hepato-toxicity, yellowish-brown discoloration of teeth if given to growing puppies or pregnant bitches

Clinical applications:

- Commonly used in treating brucellosis, usually in combination with rifamycin or streptomycin
- As feed additives (growth promoters)

1- Ruminants:

- bovine pneumonia, lower respiratory tract diseases, pasteurella haemolytica pneumonia in sheep, brucella abortis in cows, brucella ovis, brucella melitensis in sheep, closteridial infections, listeriosis, babesia divergens, thielleria parva, anaplasmosis, rickettsial diseases in lambs

2- Horse:

- Limited use
- Urinary tract infections, metritis, mastitis, prostatitis, broncho-pneumonia

3- Poultry:

- Chlamydiosis, CRD (M. gallisepticum), fowl cholera (P. multocida)

4- Dog and cat:

- Brucella canis, urinary tract infections caused by P. aeruginosa by higher urine concentrations attained
- Chlamydial infections of upper respiratory tract in cats
- Prostatic infections

5- Swine:

- Lower respiratory diseases (M. hypopneumoniae, P. multocida pneumonia)
- Leptospira infections

II- Chloramphenicol

Source:

- Obtained from streptomyces venzuelae
- Is a derivative of dichloracetic acid

Mode of action:

- Act by binding with the bacterial 50S ribosomal subunits, thus inhibiting the incorporation of amino acids into the peptide chain, and thus inhibiting the bacterial protein synthesis

Anti-microbial activity:

- Bacteristatic, broad spectrum antibiotic
- Can be bactericidal against some bacteria at high concentrations
- Effective against G+ve and many G-ve bacteria, all anaerobic bacteria, some species of mycoplasma, some species of rickettsia and some species of chlamydia

1- Good susceptibility against:

- G+ve aerobes as: actinomyces pyogens, bacillus anthracis, corynebacterium pyogens, listeria monocytogen, many staphylococcal & streptococcal species
- G-ve aerobes as: Enterobactericae (E. Coli, salmonella, klebsiella, heamophilus, pasteurella), brucella
- All anaerobes as: bacteroid fragilis, C. perferengens
- Some mycoplasma as: M. bovis, M. gallisepticum

- Some species of chlamydia
- Some species of rickettsia

2- Moderate susceptibility against:
- Leptospira species

3- Resistant:
- Mycobacteria species, nocardia
- Acquired resistance in some enterobactericae (E. Coli, klebsiella, P. aeruginosa)

Pharmacokinetics:

Absorption:
- Good after IV or deep IM injection
- Good from GIT in mono-gastric animals (dog and cat), but destroyed or in-activated in ruminants by rumen bacteria

Distribution:
- Widely distributed in all body tissues and cross all cellular barriers including CSF, CNS and aqueous humor
- Cross the placenta and reach the fetus
- Relative poor penetration of blood prostatic barrier even if the prostate inflamed

Metabolism:
- By conjugation with glucuronic acid in the liver

Excretion:
- Mainly by hepatic metabolism & small fraction (5-15 %) excreted unchanged in urine

Drug interactions:

- Should not used concurrently with bactericidal drugs (as PCNS, CSPNS, AMGS) in treating infections in which host defenses are poor because it interfere with actions of these drugs ….. antagonistic effect
- Inhibit the hepatic microsomal enzymes, thus ↓ the hepatic metabolism of co-administrated drugs with chloramphenicol (as dicoumarol & barbiturates), thus prolong and potentiate the effect of these drugs

Resistance:

- Certain types of microorganisms produce chloramphenicol acetyl transferase "CAT" (acetylase) enzyme which destroy or in-activate the drug
- Acquired resistance in some enterobactericae (E. Coli, klebsiella, P. aeruginosa)

Adverse effects and toxicity:

1- In humans:

- Bone marrow depression causing aplastic anemia
- Gray baby syndrome in newborn infants due immature developed biotransformation and excretory mechanisms. Characterized by:
  - ♣ Ashen-grey colored skin
  - ♣ Vomiting
  - ♣ Cyanosis and blue lips & skin
  - ♣ Hypotension and cardiovascular collapse
- Super-infections

2- In animals:

- Cats: are very sensitive to toxicity with chloramphenicol due to their lack of glucuronyl transferase enzyme.
- In dog and cat: therapeutic doses for longer than 7 days caused anorexia, depression, hypersensitive reactions, vomiting and diarrhea
- In calves: oral therapeutic doses lead to mal-absorption, diarrhea. Rapid IV therapeutic doses lead to severe hypotension
- In large animals: rapid IV infusion may lead to collapse, hemolysis and death

Clinical applications:

During treatment with chloramphenicol:

- Avoid overdose
- Course of therapy is limited to 7 days
- Dose ↓ for newborn animals
- Dose ↓ for patients with impaired liver function
- Avoid its use in presence of bone marrow depression

Apart from its bacteristatic properties and low activity, it has advantages of ideal antibiotics for animals are:

- Diffuses rapidly into tissues including brain, CSF and aqueous humor of eye
- Relatively non toxic
- Low costs in comparison to other agents
- Broad spectrum activity

Two problems concerned with human health and limit its use in animals are:

- Producing fatal aplastic anemia, thus restrict its use in food-producing animals
- Drug resistance

❖ Thus used only for local treatment

1- In humans:

- Is the drug of 1st choice for human typhoid fever (enteric fever) … typhoid and paratyphoid caused by Salmonella typhi
- Bacterial meningitis caused by H. infleunza

2- In animals:

- Bacterial meningitis
- Dog prostatic infections caused by G-ve organisms
- For dog and cat: otitis externa, mastitis, pyelonephritis, prostatitis, salmonellosis, canine tracheo-bronchitis

III- Thiamphenicol

- Is a derivative of chloramphenicol with similar anti-bacterial activity (but less active), absorption and distribution
- Unlike chloramphenicol, excreted unchanged in urine, thus its excretion not affected by liver diseases and by the use other drugs metabolized in liver
- Not cause aplastic anemia (safer than chloramphenicol)
- There is complete cross resistance with chloramphenicol
- Resistance occur due to presence of chloramphenicol acety-transferase enzyme in the resistant bacteria

IV- Florfenicol

- Is a fluorinated derivative of thiamphenicol
- More active than chloramphenicol
- Fluorine atom prevent its acetylation by chloramphenicol acety-transferase enzyme
- Not cause bone marrow depression or aplastic anemia (safer than chloramphenicol)

Polypeptide antibiotics

I- Polymyxins

- Are products of bacillus polymyxa
- Of greater activity against Pseudomonas aeruginosa
- **5** groups of polymyxins: A, B, C, D and E, of which only **2** used therapeutically (ploymyxin B & E) & the other groups are not used due to their severe nephrotoxic effects

Polymyxin-B:

- Known simply as polymyxin
- Obtained from bacillus polymyxa

Polymyxin-E:

- Known as colistin
- Obtained from bacillus colistinus

Mode of action:

- Are bactericidal, surface-active agents act by inhibiting the bacterial cell membrane function (permeability) by attaching to host bacterial cell membrane and:
  - ♣ Disturb the structure of the cell membrane phospholipids (endotoxins) (**i.e.** inactivate endotoxins) and,
  - ♣ Disturb the osmotic properties and transport mechanism of the cell membrane, thus ↑ the permeability of bacterial cell membrane leading to leakage of bacterial cell components and death

- G-ve bacteria are more sensitive than G+ve because the cytoplasm and outer membrane of G-ve contain larger amounts of phospholipids than G+ve bacteria

Anti-microbial activity:

- Bactericidal, highly effective against many species of G–ve bacteria as P. aeruginosa, E. Coli, salmonella, pasteurella, klebsiella, haemophilus
- G+ve bacteria are resistant
- Not effective against viruses, yeasts and protozoa

Resistance:

- Acquired resistance among P. aeruginosa due to ↓ bacterial permeability
- Complete cross resistance among polymyxins but not with other antibiotics

Pharmacokinetics:

- Topical and oral applications are more common routes
- Absorption is very slow orally and good parentrally (IM)
- Poor distribution through biologic membranes, not pass the CNS and CSF even if meninges are inflamed
- Slowly excreted unchanged in urine, and also in bile and feces

Drug interactions:

- Polymyxins (especially colistin) are synergistic with sulfonamides & trimethoprim against many resistant G–ve bacteria (including P. aeruginosa)

Adverse effects and toxicity:

- Well tolerated orally and locally
- Colistin is less toxic than polymyxin B when used systemically
- Should avoided parentrally in animals due to toxicity

1- Systemic use leads to:
  - Serious nephrotoxic effect (potentiated by AMGS)
  - Neurotoxic effect …. muscle weakness, loss of sense in extremities
  - Neuromuscular blocking effect …. can not reversed by neostigmine

2- Local irritation at site of IM injection:
  - Because they are potent histamine releasers ….. Pain & necrosis

Clinical applications:

- Not recommended systemically due to nephrotoxicity
- Major applications in:
  1- Oral treatment of E. Coli (colibacillosis) & salmonella diarrhea (salmonellosis) in calves
  2- Local or systemic treatment of coliform mastitis in cattle
  3- Local for treating superficial infections of eyes caused by resistant klebsiella or P. aeruginosa in horses
  4- Local for treating superficial infections of eyes and otitis externa and local pseudomonas infections in pet animals (dog and cat)

II- Bacitracin

- Obtained from bacillus subtilis
- Act by inhibiting the formation of peptidoglycan chain, thus preventing the bacterial cell wall synthesis
- Is bactericidal, active mainly against G+ve bacteria especially skin pathogens, staphylococci and streptococci
- Not absorbed orally or topically, absorbed parentrally but highly nephrotoxic and thus used only topically for skin topical infections caused by S. aureus and streptococci
- Synergistic with AMGS and polymyxin-B

Used as:

1- Growth promoter (zinc bacitracin) as food additive in poultry, cattle and swine
2- Prevent and treat C. perferengens enteritis in poultry, calves and pigs
3- Prevent and treat C. spiroforme enteritis in rabbits

Lincosamides and Macrolides

These antibiotics share many properties:

- Have similar pharmacokinetic properties (high lipid solubility, wide distribution in the body, capacity to penetrate cellular barriers)
- Have common site of action on the 50S ribosome
- Are bacteristatic drugs
- Active against G+ve bacteria, mycoplasma and anaerobic bacteria
- Most aerobic G–ve bacteria are resistant

I- Lincosamides (Lincomycin and Clindamycin)

- Lincomycin: is a fermentation product of streptomyces lincolensis
- Clindamycin: is a derivative of lincomycin

Mode of action:

- Bacteristatics, act by binding to the bacterial 50S ribosomal subunits and inhibiting the peptidyl transferase enzyme and thus inhibiting the bacterial protein synthesis

Antimicrobial activity:

- Are moderate spectrum antimicrobial drugs
- Clindamycin is several times more active than lincomycin
  1- G+ve aerobes as staphylococci, streptococci (but not enterococci as Str, fecalis), bacillus species, corynebacterium species

2- Few G–ve bacteria as brucella, leptospira, H. influenza, P. heamolytica
3- Anaerobes as actinomyces species (A. pyogens), C. perferengens (but not other closteridial species)
4- Mycoplasma

- Clindamycin is active against toxoplasma and certain malarial parasites
- Resistant: most aerobic G–ve bacteria (E. Coli, klebsiella, P. multocida, pseudomonas), enterococci, mycobacterium species, nocardia

Resistance:

- Occur due to: impermeability or methylation of the ribosomal binding site of lincosamides, thus prevents drug binding to the target site
- There is cross resistance between lincosamides
- Cross resistance with macrolides is common

Pharmacokinetics:

- Good absorption orally from intestine (↓ by food)
- Pass the blood brain barrier only in case of meningitis
- Penetrate well into the prostate and eye
- Excreted mainly by hepatic metabolism and about 20 % excreted unchanged in urine

Drug interactions:

- Their combination with macrolides and chloramphenicol is antagonistic in vitro (all compete for the same common binding site)
- Lincomycin, is synergistic with spectinomycin (lincospectin) against Mycoplasma in vitro

Adverse effects and Toxicity:

- The major toxic effect is their ability to cause serious and fatal diarrhea in humans, horses, rabbits
- Cause disturbance of normal GI microflora, thus predisposes to colitis
  1- Cattle: diarrhea
  2- Horse: fatal diarrhea and heamorrhagic colitis
  3- Rabbits: highly toxic, fatal diarrhea, heamorrhagic colitis
  4- Dogs and cats: relatively non toxic, vomiting and diarrhea orally, cardiac depression by rapid IV injection, anaphylactic shock by IM route

Clinical applications:

1- Ruminants:

- Respiratory diseases (lincospectin)
- Acute or chronic foot rot in sheep (lincospectin)
- Staphylococcal or streptococcal mastitis

2- Swine:

- Dysentery and mycoplasma (pneumonia) infections (lincomycin)

3- Horses:

- Should not used because of their toxicity
- Staphylococcal & streptococcal infections

4- Dog and cat:

- Staphylococcal & streptococcal infections (abscesses, wounds) (lincomycin)
- Toxoplasma infection (clindamycin)
- Prostate and eye infections (clindamycin)

5- Poultry:

- CRD caused by mycoplasma and E. Coli (lincospectin)

II- Macrolides antibiotics

1- Erythromycin

- Obtained from streptomyces erythreus

Mode of action:

- Bacteristatic, act by binding to the bacterial 50S ribosomal subunits and inhibiting the peptidyl transferase enzyme and thus inhibiting the bacterial protein synthesis

Antimicrobial activity:

- Good susceptibility against:
  - G+ve aerobes as staphylococci, streptococci, bacillus species, corynebacterium species, listeria species
  - Few G–ve bacteria as actinobacillus species, brucella, leptospira, heamophilus species, pasteurella species
  - Anaerobes as actinomyces species (A. pyogens), closteridia species
- Resistant: enterobacteriacae, pseudomonas, mycobacterium species, nocardia

Resistance:

- Occur due to: impermeability and methylation of the ribosomal binding site of erythromycin, thus prevents drug binding to the target site
- There is cross resistance between macrolides
- Cross resistance with lincosamides is common

Administration:

- Oral and parenteral
- Parenteral caused tissue irritation at the site of injection

Drug interactions:

- Its combination with lincosamides and chloramphenicol is antagonistic in vitro (all compete for the same common binding site)
- Used alone or with AMGS to prevent or treat peritonitis after intestinal spillage but not effective as clindamycin or metronidazole in combination with AMGS

Adverse effects and Toxicity:

- The major toxic effect is its ability to cause serious and fatal diarrhea in horses and rabbits and cause disturbance of normal GI microflora, thus predisposes to colitis
- Thus, should not used in horses especially adult
- No deaths reported in horses but in rabbits
- Safe in dog and cat
- All macrolides shared in their irritating nature which leads to:
  - Severe pain after IM injection
  - Thrombophlebitis after IV injection
  - Cellular reactions after I/mammary administration

Clinical applications:

Ruminants:

- Respiratory diseases caused by H. somnus, A. pyogens
- Campylobacter enteritis and diarrhea
- Lactating and dry-cow therapy of mastitis

Horses:

- Should not used because of their toxicity
- Staphylococcal & streptococcal infections

Dog and cat:

- Staphylococcal & streptococcal infections (abscesses, wounds)
- Campylobacter enteritis and diarrhea

Poultry:

- CRD caused by mycoplasma and E. Coli
- Staphylococcal & streptococcal infections
- Infectious coryza

2- Tylosin

- Obtained from Streptomyces fradiae
- Antimicrobial activity: similar to erythromycin, but more active against a broad range of mycoplasma
- Resistance, drug interactions, adverse effects and toxicity: similar to erythromycin

Clinical applications:

- Mainly mycoplasma infections especially pneumonia

Ruminants:
- Infections caused by mycoplasma (pneumonia, arthritis)
- Campylobacter enteritis and diarrhea
- Acute or chronic foot rot in sheep
- Staphylococcal & streptococcal mastitis

Horses:
- Should not used because of their toxicity

Dog and cat:
- Staphylococcal & streptococcal infections (abscesses, wounds)
- Upper respiratory tract infections (mycoplasma pneumonia)

Swine:
- Used as growth promoter

Poultry:
- CRD caused by mycoplasma and E. Coli
- Staphylococcal & streptococcal infections
- Avian spirochetosis

3- Spiramycin (Rovamycin)

- Obtained from streptomyces ambofaciens
- Is several times less active against bacteria than erythromycin, but
- It is not as effective against mycoplasma as tylosin
- Has the same applications of tylosin in ruminants, swine and poultry

4- Tilmicosin

- Long-acting macrolide for use in bovine respiratory disease because of its activity against pasteurella heamolytica and A. pyogens, H. somnus and mycoplasma
- A single SC dose of 10 mg/kg leads to lung concentrations exceeding the MIC of pasteurella heamolytica for 72 hours
- It is not approved for use in lactating cattle
- Also, not approved or recommended for use in horse, sheep or goat by any route, because of toxicity

5- Tulathromycin

- Is a semisynthetic long acting macrolide for respiratory infections
- Effective against G+ve bacteria as streptococcus pneumonia, heamophilus influenza, mycoplasma
- Highly cardiotoxic on rapid IV injection and may caused death, thus should injected slowly

- Clinical applications:
  - **1-** Bovine respiratory disease (BRD)
  - **2-** Infectious bovine kerato-conjunctivitis (IBK)
  - **3-** Foot rot in beef and non-lactating dairy cattle
  - **4-** Swine respiratory disease (SRD)

6- Tylvalosin (Aivlosin)

- Synthetic water soluble granules
- For use only in the drinking water of pigs
- Not for use in lactating or pregnant
- For treating enteritis and diarrhea in pigs
- Preparation: AIVLOSIN® (62.5% w/w Tylvalosin as Tylvalosin Tartrate)

Sulphonamides

****

Definition:

Sulphonamides are synthetic organic compounds with chemotherapeutic activity.

History:

Sulphonamide was first synthesized by Glmo, 1908 Then it was first sulphonamide (prontosil) by Domagk in 1935. Sulphonamide, was synthesized, 1936, was less toxic than prontosil. Pyramidine sulphonamides including sulphadimidine, sulphadiazine and sulphamerazine was discovered lately then antibiotics. The value of the sulphonamide was decreased by wide spread nature of acquired resistance. Whereas combination with trimethoprim or ormetoprim enhanced their usefulness.

Physical properties:

1-They are white slightly bitter powder.

2-They are hardly soluble in water, while their sodium salts are soluble and in the body decompose and release sulphonamides.

Route of administration:

1-Per Os: It is the main route, because it readily absorbed from the GIT.:
although their sodium salts could be given I/V for systemic action.

2-Locally:For local action insoluble sulphonamides are taken by mouth to produce local effects in the intestine.

3-Externally:Sulphonamides can be applied locally e.g.---sulphacetamide sodium, which is the only one that given for local application to the eye.

N.B.:

1-Na.salts of sulphonamides are highly alkaline. (pH 9-10.2) so they can not be given S/C or I/M for they saponify S/C fat and cause necrosis.

2-Application of sulphonamide externally they retard healing.

Chemistry:

Sulphonamides are derivatives of sulphanilamide. They differ in the radical (R) attached to the amide ($-SO_2$ NHR) group or in the substituent on the amino (-NH2) group (Fig. 1)

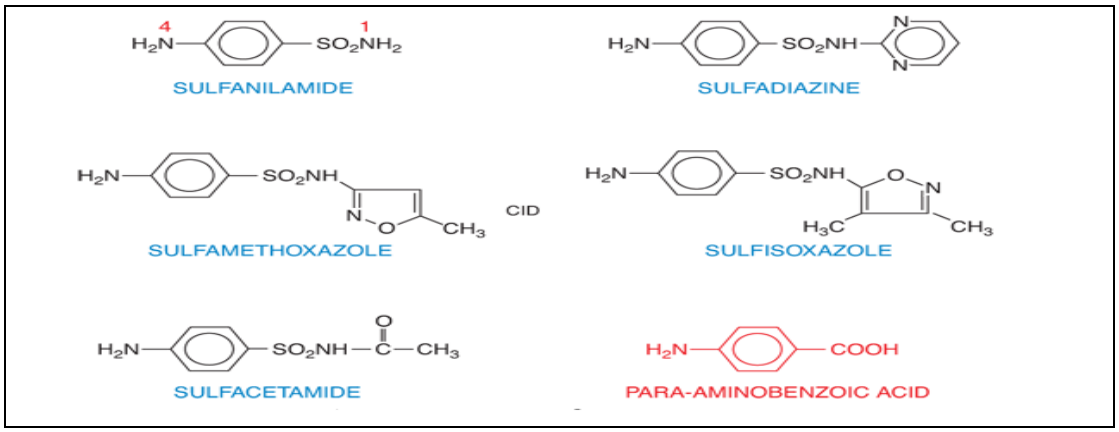

Fig. (1): Structural formulas of some sulfonamides

The derivatives of sulphonamides differ in:

1-physicochemical properties. 2-their pharmacokinetic

3-degree of antimicrobial activity. 4-they are more soluble at alkaline than at acid pH. But as group sulphonamides are quite insoluble.

5-sodium salts of sulphonamides are soluble in water and I/V injection is the parentral preparation. These solutions are highly alkaline in reaction with exception of Na sulphacetamid, is neutral as an ophthalmic preparation. Whereas certain sulphonamide molecules, has low solubility as they slowly absorbed and intended for use in the treatment of enteric infections.

Pharmacokinetics of sulphonamides

1-Absorption:

The absorption of soluble sulphonamides is completely from the GIT within 4 hours. The rate of absorption depends on the species of animals:-

a-in case of dogs the rate of absorption is rapidly and completely.

b-in case of horse " " " " " moderate.

c-in case of cattle " " " " " longer.

The sulphonamides constitute a series of weak organic acids with pKa values ranging from 10.4 for sulphanilamides to 5.0 for sulphasoxasole. They exist predominantly in the nonionized form in biologic fluids of pH that lower than their pKa. It is the non ionized moiety that diffuses through cell membranes and penetrates cellular barriers.

2-Distribution:

a-After absorption, sulphonamides are distributed in all tissues and body fluids with different levels.

b-Sulphonamides are readily reach to the cerebrospinal fluids and also pass through the placenta.

c-The distribution of sulphonamides was less in the brain, bones and fats.

d-The sulphonamides are bound to plasma proteins 15-90 % There is variation among species in binding of individual sulphonamides.

e-Extensive(> 80 %) protein-binding increases half-life.

f-In any one species, the extent of protein binding apparent volume of distribution and half-life vary widely among individual sulphonamides.

3-Metabolism:

1-Sulphonamides undergo metabolic alterations to a variable extent in the tissues, especially the liver.

2-Acetylation which is the principal metabolic pathway for most sulphonamides.

3-Glucuronide conjugation & aromatic hydroxylation take place in all domestic animals except dogs. It appears that dogs can not acetylated aromatic amines.

4-Acetyation takes place in the reticulo-endothelial rather than the paranchymal cells of the liver and other tissues such as the lungs. Acetylation increase the risk of damage to the renal tubules due to precipitation.

5-Aromatic hydroxylation, which may be the principal metabolic pathway for sulphonamide in ruminants and glucuronide conjugation are microsomal-mediated metabolic reactions. The glucuronide conjugates are highly water soluble and are rapidly excreted.

6-After binding to plasma protein, sulphonamids are gradually released to free sulphonamides under which the bacteriostatic effect of its different members.

N.B: The metabolized sulphonamides (acetylated) has the following characters :

No antibacterial activity, toxic and less soluble than the original compounds.

4-Excretion:

a-Renal excretion mechanism include glomerular filtration of free drug in the plasma, active carrier-mediated proximal tubular excretion of ionized unchanged drug and metabolites and passive re-absorption of non ionized drug from distal tubular fluid. The extent of re-absorption is determined by the pKa of the sulphonamide and the pH of the fluid in the distal tubules.

b-The sulphonamides are more soluble in alkaline than in acid urine and their concentration in the urine is 10-20 times than in the blood.

c-In acid urine, the free and acetylated derivatives may precipitated in the renal tubules and this may lead to renal colic, haematurea and enhanced toxicity.

d-Renal impotency leads to higher sulphonamide level in the blood and toxicity may occur.

N.B: In Vet. Practice, there is no need to use alkaliners, because in dogs acetylation does not occur and in herbivore, urine is normally alkaline.

Mode of action

1-Sulphonamides interfere with the biosynthesis of folic acid in bacterial cells: Competitively preventing para-aminobenzoic acid (PABA) from incoeporation into the folic acid molecule. Specifically sulphonamides compete with PABA for the enzyme dihydropteroate synthetase. Their selective bacteriostatic action depends on the difference between bacterial and mammalian cells in the source of folic acid. Susceptible microorganisms must synthesize folic acid, whereas mammalian cells use preformed folic acid.

2-Inhibition of carbonic anhydrase enzyme: Sulphonamides inhibit carbonic anhydrase enzyme which has several actions. One of these actions is the formation of egg shells. Hence on sulphonamides, the lay eggs has soft shells. This enzyme also helps in the secretion of hydrogen in urine. Its inhibition leads to diuresis.

Antibacterial activity

Sulphonamides are broad-spectrum antimicrobial agents, inhibiting bacteria, chlamydiae, toxoplasma and other protozoal agents such as coccidia. The MIC(minimum inhibitory concentration) of sulphonamides is markedly affected by the composition of the medium and the bacterial inoculum concentration. An MIC of 10-40 ug/ml is a reasonable definition of susceptibility for short-acting sulphonamides. An MIC of $\geq$ 100 ug/ml can be interpreted as evidence of resistance.

Bacterial resistance to sulphonamides

Sulphonamides has no effect on the following:

1-on bacteria that not require folic acid for their growth.

2-sulphonamide antagonists are: large dose of PABA, local anesthesia that contains radical PABA and folic acid

3-presence of pus and debris (pus contains large amounts of PABA).

4-repeated therapeutic dose make resistance may be due to that bacteria are able to make large amount of PABA.

Mode of resistance

Chromosomal mutation to resistance develops slowly and gradually and results from impairment of drug penetration of an insensitive dihydropteroate enzyme, or hyper-production of PABA. Plasmid-mediated resistance is for more common and is the result of impaired drug penetration or the production of additional, sulphonamide-resistant, dihydropteroate synthetase enzymes. Resistance to sulphonamides is wide spread in bacteria isolated from animals, reflecting extensive use of the drug over many years. There is complete cross-resistance between the sulphonamides.

Classification of sulphonamides

I-According to their site of action:

a-systemic or absorbable sulphonamide: e.g sulphadiazine

b-intestinal or non-absorbable sulphonamides: these are sulphonamides which are poorly absorbed from the GIT and exert their effect on the intestinal bacteria or Imeria species e.g sulphaquanidine

*sulphasuxidine….hydrolyzed in the intestine to → sulphathiazole

*sulphathalidine … hydrolyzed in the intestine to → sulphathiazole

There is no risk of toxicity in non absorbable sulphonamides

II-According to the rate of absorption and elimination:

A-Rapidly absorbed and rapidly eliminated (short-acting sulphonamides):

i-general infection (e.g…sulphadimidine, sulphadiazine)…given every 4 h

ii-urinary infection (e.g…sulphafurazole, sulphasomidine)…they are rapidly excreted by the kidney to treat tissue infection and the plasma concentration insufficiency. Acetylation is less so resulted in high concentration of the active drug. Solubility in urine is relatively high even if it is acid. Given every 4-6 h.

B-Rapidly absorbed and slowly eliminated (long-acting sulphonamides):

It is given once or twice daily. Heavy protein bound. Not used for general purposes for they provide low plasma concentration of free drugs at safe doses. e.g…..sulphadoxine, sulphamethoxine, sulphasomizole.

Drug interaction

1-synergistic action (sulph. + trimethoprim).

2-sulph. + penicillin → antagonize sulphonamides than procaine of procaine penicillin is an analogue of PABA.

3-combination of sulphonamides with pyrimethamin is the treatment of choice for toxoplasmosis

Toxicity and adverse effects of sulphonamides

1-allergic basis

2-urinary tract disturbances (crystalluria, haematuria or even obstruction), haematopoietic disorders (thrombocytopenia and leucopenia)

3-other idiosyncratic reactions reported in dogs include cutaneous drug eruptions and hepatitis

4-sulphadiazine and sulphasalazine given for long periods to dogs caused kerato-conjunctivitis sicca

5-prolonged dosage with sulpa-ethoxypyridine in dogs has produced cataracts

6-sulphaquinoxaline has caused hypothrombinemia, haemorrhage and death in puppies given the drug orally for control of coccidiosis. Haemorrhage occurs in some species due to that the drug antagonize vitamin k.

7-treatment of sulphonamide toxicity:

a-sufficient of water must be given
b-urine should be kept alkaline since the acetylated derivatives are more soluble in alkaline urine
c-with many newer sulphonamides, alkalinization is not necessary.
N.B.: sulphasiazole and sulphamerazine are more liable to cause crystalluria than most of other compounds

Administration and dosage

1-sulphonamides should be given as early as the course of disease as possible, so the more severe the infection the greater should be the dose (initial dose)
2-initial orally dose 0.2 gm/kg b.wt and maintenance dose 0.1 gm/kg b.wt for all animals
3-for chickens, in the food or drinking water sulphaquinoxaline as 0.05 % as prophylactic
4-sulphonamides should be continue in its administration for 2 days after the disappearance of the clinical symptoms otherwise bacteria multiply again and a relapse may result
5-any renal disturbance during treatment will indicate the onset of toxicity
6-the usual dosage of sulphonamides and trimethoprim-sulphonamide combination in animals (Table 1).

Table (1): usual dosage of sulphonamides and trimethoprim-sulphonamide combination in animals

Drug	Route	Dose (mg/kg)	Dosing interval (hr)	Comment
Short-acting Sulphadiazine, sulphamethazine, trisulphapyramidine (triple sulfas)	IV, PO	50-60	12	100 mg/kg priming dose
Intermediate acting	IV, SC	27.5	12-(24)	55 priming
Sulphadimethoxine	PO	55	12-(24)	100 priming
Sulphadimethoxine	PO	50	8	Urinary tract infections
Sulfisoxazole Sulphamethoxazole	PO	50	12	As above
Gut active Pathylsulfathiazole	PO	100	12	
Special use Salicylazosulfapyridine	PO	25	12	See text
Trimethoprim-sulfonamide	IV,IM	24-30	12	
Combination	PO	36	12	Meningitis (TID)

Clinical applications (therapeutic uses of sulphonamides)

Widespread resistance greatly limits the effectiveness of sulphonamides in treating bacterial diseases of animals. Trimethoprim-sulphonamide combination have largely replaced sulphonamides as therapeutic agents used in companion animals

1-cattle, sheep and goats:

a-orally administered, long acting sustained-release dosage forms results in effective plasma concentrations for 3-5 days
b-it is used experimentally in preventing of P. haemolytica pneumonia in calves
c-used in treatment of feed lot pneumonia in bovine pasteurella
d-it is used to treat bovine interdigital necrobacillosis and coccidiosis
e-sustained-release oral sulphamethazine and orally administered pyrimethamine, 0.5 mg/kg once daily, might be drugs of choice in preventing outbreaks of toxoplasma abortion in sheep
f-sulphonamides have been used with chlortetracyclines in feed-lot lambs to improve performance and prevent closteridial enterotoxemias

2-horse: sulphonamides only used in horses in combination with trimethoprim

3-dogs and cats:
a-sulphasoxazole used for treating urinary tract infections in dogs replaced by broad-spectrum of activity of bacterial actions of antibiotics
b-used in the treatment of nocardia infections
c-silver sulphadiazine cream used in the treatment in chronic otitis externa caused by multiply resistant P. aeruginosa, as the drug act as a broad-spectrum antimicrobial antiseptic
d-sulphasalazine used in the treatment of chronic colitis in dogs
e-dapsone used in the treatment of dermatitis herpetiformis in dogs
4-poultry: sulphonamides used in the treatment and prevention of coccidiosis, infectious coryza, pullorum disease and fowl typhoid.

Trimethoprim and Ormetoprim

Definition:
1-trimethoprim is a diaminopyrimidine (figure 2). A synthetic folic acid antagonist that is widely used in combination with sulphonamides. It is a weak base with pKa about 7.6 and is poorly soluble.

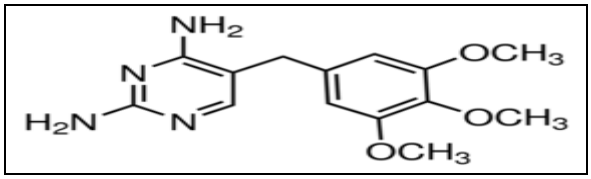

Fig. (2): Structural formula of trimethoprim

2-ormetoprim is a diaminobenzylpyrimidine closely related to trimethoprim

Mode of action:

Diaminopyrimidine interfere with the synthesis of tetrahydrofolic acid from dihydrofolate by combining with the enzyme dihydrofolate reductase.

N.B.: selective antibacterial activity occurs because of greater affinity for the bacterial rather than the mammalian enzyme. A synergistic and bactericidal effect occurs when the diaminopyrimidines are combined with sulphonamides.

Antimicrobial activity:

Trimethoprim is bacteriostatic, broad-spectrum drug active against G+ve and G-ve aerobic bacteria. Bacteria with an MIC of 1 ug/ml or below regard as sensitive

Resistance:

Resistance to trimethoprim and other diaminopyrimidine is usually the result of transposon-encoded plasmid or chromosomal synthesis of a resistant dihydrofolate reductase enzyme e.g….among enterobacteriaceae. Isolates with plasmid-mediated resistance commonly show multiple resistance which includes sulphonamide resistance.

Pharmacokinetics:

Trimethoprim is a lipid-soluble organic base. 60 % ionized and 60 % bound to the plasma protein. The drug distributes widely, penetrating cellular barriers by nonionic diffusion and attaining effective concentrations in most body tissues and fluids. The drug may concentrate in fluids such as the prostate. The average ratio concentration of milk to plasma is 3:1. metabolism of trimethoprim in the liver oxidation followed by

conjugation reactions. The elimination and half-life of trimethoprim that excreted unchanged differ among species as in table (2).

Toxicity and adverse effects:

It is non toxic. It induce deficiency of folic acid at high doses.

Table (2): Half-life and urinary excretion of trimethoprim

Species	Half-life (hr)	Dose excreted unchanged in urine (%)
Human	10.6	47
Horse	3.8	10
Dog	3.0	20
Pig	2.0	16
Cow	1.0	3
Goat	0.7	2

Clinical applications:

Trimethoprim alone or incombination with a drug of choice for treating prostatic infection caused by G-ve bacteria since prostate concentrations may reach 10 times those of plasma at this concentration the drug may be bactericidal. It is used for treating pneumonia.

Trimethoprim (TMP)-sulphonamide

Ormetoprim-sulphonamide combination

Trimethoprim, ormetoprim or aditoprim are combined with a variety of sulphonamides (sulphadiazine, sulphamethoxazole and sulphadoxine) in fixed ratio 1:5. the combination produces a bactericidal effect against a wide range of bacteria.

Veterinary preparations:

TMP+sulphadiazine (ratio 1:5) and TMP+sulphadoxine (ratio 1:5)

Mode of action:

The combination of diaminopyrimidine with a sulphonamide inhibits sequential steps in the synthesis of folic acid and thus of the purines required for DNA synthesis. The interference by the aminopyrimidine methoprim with recycling of tetrahydrofolic or dihydrofolic acid probably responsible for the synergistic interaction of the combination.

Antimicrobial activity:

1-trimethoprim-sulphonamide have broad spectrum bactericidal against G+ve and G-ve aerobic bacteria including enterobacteriaceae

2-synergism occurs when the microorganisms are sensitive to both drugs. It may be obtained in up to 40 % of the cases when bacteria are resistant to sulphonamides. Synergism often occurs if the organism is resistant to trimethoprim but sensitive to sulphonamides and in nearly 40 % of cases in which the organism is resistant to each drug alone.

3-where synergistic interaction a 10-fold increase in the activity of the trimethoprim component.

4-good susceptibility (MIC $\leq$ 0.5/9.5 ug/ml) for G+ve. Moderate activity (MIC $\leq$ 2/36 ug/ml) some mycobacterium sp. Resistance (MIC $\geq$ 4/72 ug/ml) rickettsia sp.

Resistance:

Multiply resistant R factor which include both sulphonamide and trimethoprim resistance, have been reported in salmonella typhimurium and enterotoxigenic E.Coli isolated from animals.

Toxicity and adverse effects:

1-in horse: IM injection leads to minor tissue damage and pain, transient pruritis for the 1st injection only. IV injection may leads to respiration failure

2-in dogs: vomiting, diarrhea, polydipsia, polyuria, facial edema, salivation, elevated liver enzyme levels and jaundice, bilateral keratoconjunctivitis sicca. Idiosyncratic reactions (fever, polyarthritis, joint pain). Occurs in number of breeds of dogs.

Administration and dosage:

Dose: 24 mg/kg of the combination IM at 12 h intervals

Clinical application

In the treatment of: urinary tract infections, bacterial prostatitis (because of good tissue penetration), brucellosis, mycobacterial infection, enteric infections, respiratory infections

Cattle, sheep and goats:

In calf salmonellosis and diarrhea caused by enterogenic E. Coli. In bacterial pneumonia and in foot rot and in septicemic colibacillosis. In meningitis give the drug IV for times daily at usual dosage. In acute mastitis the drug given IV at dose 48-50 mg/kg every 12 h. in case of urinary tract infections and metritis. In case of toxoplasma abortion in sheep and prevention of clamydial abortion.

Horses:

In case of acute respiratory infections including strangles, acute urinary tract infections and wounds and abscesses. Also in salmonellosis. In foals in actinobacillosis and coliform infections. In meningitis 3-4 times daily slowly I/V. In protozoal encephalomyelitis in combination with pyrimethamine

Dogs and cats: it is used against specific and non specific infections

Poultry:

Trimethoprim-sulphaquinoxaline used for prophylaxis and treatment of E. Coli, haemophilus and pasteurella infections as well as coccidiosis at a dosage of 30 mg/kg/day/ ratio 1:3 sulphamethoxasole-ormetoprim in also used against fowl cholera and coccidiosis in poultry.

OTHER ANTIMICROBIALS

I-Quinolones

Quinolones are a series of synthetic antibacterial agents. First introduced in 1964 was nalidixic acid. It was the 1st generation quinolones which includes nalidixic acid, flumequine and oxilinic acid showed activity against G-ve bacteria. And used in the treatment of urinary and enteric infections.

Topoisom-erase inhibitors/ quinolon-es/inhibit DNA replication	**Fluoro quinol ones**	**1st generation**	**flumequine,naldixic acid, oxolonic acid, pipemidic acid, piromidic acid, rosoxacin**
		2nd generation	**ciprofloxacin, enoxacin, ofloxacin, fleroxacin, lomefloxacin, nadifloxacin, pefloxacin, norfloxacin, rufloxacin**
		3rd generation	**balofloxacin, levofloxacin, grepafloxacin, pazufloxacin, sparfloxacin, temafloxacin, tousfloxacin**
		4th generation	**besifloxacin, clinfloxacin, moxifloxacin, gatifloxacin, gemifloxacin, sitafloxacin, garenoxacin, trovafloxacin/alatrofloxacin**
		Veterinary	**danofloxacin, enrofloxacin, marbofloxacin, difloxacin, ibafloxacin, orbifloxacin, sarafloxacin, pradofloxacin**

First generation of the quinolones include the following

A-Flumequine

It is an original synthetic quiolone. It is effective bactericidal against G+ve and G-ve bacteria. Its action occurred by inhibiting the protein biosynthesis of nucleic acid of bacteria. Its therapeutic uses in prevention and treatment of respiratory and digestive diseases of poultry caused by bacteria.

5-Its pharmacokinetics (water soluble, rapidly absorbed from GIT and widely distributed and excreted with urine).

Dosage: for prevention 25 mg/100 L water. for treatment 25 mg/100 L for 3-5 day.

7-Contraindication for using flumequine with nitrofurans and trimethoprim.

B-Nalidixic acid

It is antibacterial drug against G-ve bacteria affecting mainly GIT and urinary tract of poultry and young animals.

Side effects: It may cause vomition and jaundice.

Contraindication for using with nitrofurans.

Dosage: For poultry (1 gm/L of water or 2 kg/ton feed). For calves (1-3 gm daily).

C-Oxolinic acid

It has a bactericidal action against G-ve bacteria by inhibiting DNA synthesis. It is rapidly absorbed via orally administration as 5 % solution of the acid or its Na salt. It is using mainly for poultry colibacillosis. CRD, enteritis, cholera and coryza. Also the drug used for treatment genital colibacillosis in laying hens.

4-Dosage:-40 mg/100 kg of body weight per day for 5 days.

2-Second-generation quinolones (fluoroquinolones)

which included in this group are enrofloxacin, danofloxacin, ciprofloxacin, norfloxacin and ofloxacin.

Mode of action:

Fluoroquiolones inhibit the activity of bacterial DNA gyrase, an enzyme which controls the supercoiling of DNA by converting relaxed covalently closed circular DNA to a superhelical form by an energy-dependent strand breakage and releasing process. The effect of preventing releasing following breakage is to degrade chromosomal DAN and to produce a bactericidal effect on the cell because exonucleases degrade DNA exposed in this maner. The bactericidal action of fluoroqinolones is both rapid and concentration-dependent. Activity is inhibited at very high concentrations through direct inhibition of RNA synthesis and can be antagonized by protein synthesis inhibitors(chloramphenicol) and RNA synthesis inhibitors (rifampin).

Antimicrobial activity:

Fluoroquinolones are highly active against G–ve aerobes including Enterobacteriaceae but useful therapeutic active against G+ve aerobes (Table 3). The drugs are relatively inactive against anaerobes. Ciprofloxacin and ofloxacin have important activity against mycobacteria. Fluoroquinolones are active against mycoplasma and rickettsia. In-vitro activity is affected by pH, with activity decreasing below pH 7.0 and increasing above pH 7.4. Activity in urine may be reduced as may activity in phagocytes or abscesses. Fluoroquinolones penetrate phagocytic cells well. Good susceptibility (MIC $\leq$ 1 ug/ml), Moderate, variable susceptibility (MIC 1-4 ug/ml) and resistant (MIC $\geq$ 4 ug/ml) bacteria include anaerobic bacteria and pseudomonas maltophilia.

Resistance:

Resistance occurs through single-step mutation at a low frequency, less than nalidixic acid and related early quinolones. High-level, stable resistance can occur by progressive exposure to increasing subinhibitory drug concentrations. Mutations producing resistance occur in the A subunit of the DNA gyrase or in bacterial permeability, the latter sometimes producing cross resistance to unrelated drugs, including newer beta-lactams. Plasmid-mediated resistance is not occur.

Pharmacokinetics:

Fluoroquinolones are rapidly and completely (80-100 %) absorbed after oral administration to monogastric animals except norfloxacin (40 %) and ciprofloxacin (50-70 %). Peak concentration occurs after 1-2 hours. Whereas in case of ruminant the absorption is poor after oral administration. Distribution is

wide spread, they penetrate well into cerebrospinal fluid, bronchial secretions, bone and cartilage and prostatic tissues. Prostatic tissue concentration is up to twice those of the serum. High concentrations are founds in the organs of excretion (liver, bile, urinary tract). Fluoroquinolones are metabolized in the liver inducing number of metabolites and are excreted in the urine or bile as active drug. Urinary drug concentrations exceed serum concentration by several hundred times and remain high for 24 hours after administration.

N.B.: Reduction of dosage is required in patients with impaired renal function. Bile concentration are 2-10 times serum concentrations and enterohepatic recycling may occur.

Elimination half-life varies with different species and different fluoroquinolones as follows: plasma half-life for enrofloxacin was (3-5 h) after S/C injection, but in calves it was 5-6 h. elimination half-life for ciprofloxacin in dogs 3-5 h after oral administration and for norfloxacin is 6 h.

Table (3): Susceptibility (MIC90, ug/ml) of selected veterinary pathogens to ciprofloxacin, danofloxacin, enrofloxacin and norfloxacin

organism	Ciprofloxacin	danofloxacin	Enrofloxacin	Norfloxacin
G+ve aerobes				
A. pyogens	1		1	8
E. rhuseopathiae	0.06	0.15	0.06	0.125
C. pseudotuberculosis	0.06		0.125	0.5
L. monocytogenes	2		2	8
R. equi	1		1	8
S. aureus	0.5	0.2	1	1
S. agalactiae	1		1	4
S. equi	1	0.8	1	8
G-ve aerobes				
A. pleuropneumoniae	0.007	≤ 0.05	0.015	0.03
B. bronchoseptica	2	1.6	4	8
C. jejuni	0.25		0.25	1
E. Coli	≤ 0.03	0.4	0.5	0.12
H. somnus	0.015		0.015	0.125
Klebsiella	0.12		0.5	0.5
P. haemolytica	0.03			
P. multocida	0.02	≤ 0.05	0.12	0.13
P. vulgaris	0.06		0.5	0.12
P. aeruginosa	1	0.4	2	2
Salmonella sp.	0.03	0.03	0.5	0.06
Yersinia sp.	0.02		0.04	0.13
Anerobes				
Bacteroides sp.	16	> 25		≥ 64
Closteridium sp	8			≥ 64
Fusobacterium sp.	8	12.5		≥ 64
Peptostreptococcus sp.	8			≥ 64
Mycoplasma				
M. bovis	0.25	0.2	0.5	
M. gallisepticum	≤ 0.03	≤ 0.5	1.0	
M. hyorhinis		0.2	1.0	
M. hyopneumoniae		0.06	≤ 0.03	

Drug interaction:

1-The fluoroquiolones show little or no synergism or antagonism with beta-lactam, macrolide or aminoglycoside antibiotics. The combination with these drugs produce additive effects.

2-There are antagonistic interaction between fluoroquinolones and nitrofurans and with chloramphenicol.

3-Fluroquinolones used with metronidazole to expand the antibacterial spectrum of combination.

4-Clearance of other drug metabolized in the liver (e.g.theophylline) might be reduced by concurrent administration with fluoroquinolones.

5-Magnesium and aluminium reduce the absorption of fluoroquinolones from the intestinal tract.

Toxicity and side effects:

1-Fluoroquinolones are considered to be relatively safe drugs.
2-Side effects appear in dogs as erosion of weight-bearing cartilage sufficient to euthanasia on human grounds
3-in horse: use is not recommended because of potential arthralgic effects
4-caution in use of these drugs should be exercised with the young of other species.

Administration and dosage:

1-Fluoroquinolones are given orally in momogastric animals whereas in ruminants (IM, SC), (Table 4).

Table (4): usual systemic dosages of currently available fluoroquinolone in animals

Species	Drug	Route	Dose (mg/kg)	Interval (hr)	Comment
Dogs, cats	Norfloxacin Enrofloxacin Ciprofloxacin 	PO PO IM PO PO	22 2.5 2.5 5-8 10-15	12 12 loading dose 12 12	Dogs not < 8 Months of Age As above, urinary tract, Soft tissue, bone (not approved)
Cattle, sheep, goats	Enrofloxacin	PO IM, SC	2.5-5 2.5-5	24 24	Pre-ruminants Ruminants
Swine	Enrofloxacin	IM, PO	2.5-5	24	
Poultry	Enrofloxacin	PO IM	50 ppm 0.5 mg/bird	Water SID	 Turkey, salmonella

Note: other fluoroquinolones will be licensed for animal use in the near future, including danofloxacin for food animal use.

2-Lower doses may be appropriate for urinary and GIT infections
3-Norfloxacin is administered at higher dosages than ciprofloxacin or enrofloxacin.

Clinical application:

I-Cattle, sheep and goats: Natural and experimental pneumonia associated with mycoplasma bovis and pasteurella species has respond well to daily dosage of 2.5 mg/kg for 3-5 days for enrofloxacin orally or IM. Enrofloxacin or danofloxacin may be a drug of choice for pneumonia in cattle and sheep. Fluoroquinolones orally or by injection used for treatment of E. Coli and salmonella enteritis and septicemia also these drugs gave excellent potential use against mycoplasma, rickettsial and chlamydial infections in these species.

II-Horse: Because of their general potential to cause erosion of cartilage, fluoroquinolones are not recommended in horses. Enrofloxacin was administered orally (2.5 mg/kg) for treatment of chronic E. Coli and streptococcal pleuritis in an adult horse where, because of antibiotic resistance, alternative antimicrobial treatments would have been prohibitively expensive. They should not be administered to young, growing horses.

III-Dogs and cats: Fluoroquinolones have many potential applications in dogs and cats with exception to not use for young dogs of medium size under 8 months of age, nor in the larger or gaint breeds under 12-18 months of age. Among uses of fluoroquinolones are urinary tract infections including

prostatitis, respiratory tract infections, wound infections, intestinal infections and osteomyelitis caused by G-ve aerobes.

IV-Poultry: Danofloxacin and enrofloxacin are used against mycoplasma infections, erysipelas, E. Coli infections, fowl cholera and salmonellosis. IM injection of 0.5 mg/bird danofloxacin has been used in the prevention of salmonellosis in turkey.

II-Nitrofurans

Nitrofurans (figure 3) have broad antibacterial activity. They are used for treatment of intestinal and urinary tract infections as topical application.

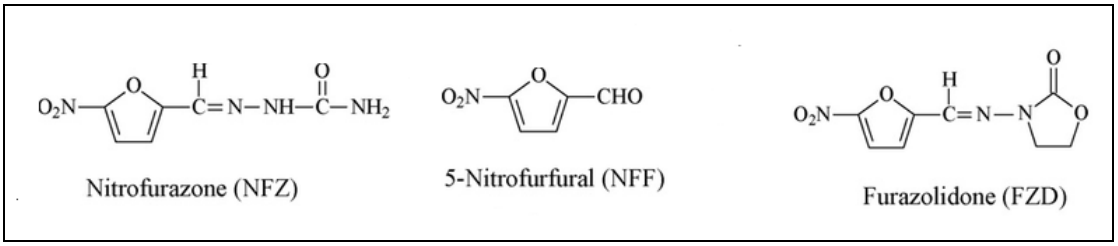

Fig. (3): Structural formulas of nitrofuran drugs

N.B.: due to the toxic effect of nitrofurans their effects are limited to use for topical application. Five compounds are used in veterinary medicine: nitrofurazone, nitrofurantoin, nifuratel, nifuroquine and furazolidone.

Mode of action:

Bacterial nitroreductase4 enzymes degrade nitrofurans to a variety of poorly characterized reduction products that differ depending on the nitrofuran involved. The antibacterial effect of nitrofurans results from these reduction products, which cause breakage of strands of bacterial DNA.

Antibacterial activity:

1-nitrofurazone, nitrofurantoin, nifuratel and furazolidone have similar antimicrobial activity.

2-they are relatively broad-spectrum drugs active against bacteria, some protozoa and some fungi.

3-nitrofurans are bactericidal at concentrations just over MIC.

4-antibacterial effect reduced by alkaline conditions but is greatly enhanced at pH 5.5 or below and diminished by very high concentration of bacteria in urine.

5-G+ve bacteria as staph. aureus, streptococci and corynebacteria and G-ve bacteria such as E. Coli and salmonella are usually sensitive to nitrofurans. Nitrofurans have moderated activity against anaerobic bacteria. Klebsiella, Proteus species and Pseudomonas aeruginosa are always resistant.

6-furazolidone has the greatest antibacterial activity followed by nitrofurazone and nitrofurantoin. The MIC_{50} of furazoildone for salmonella Dublin was 1.25 ug/ml, 10 ug/ml for nitrofurazone and 40 ug/ml for nitrofurantoin.

Resistance:

1-resistance involves aither absence of intracellular reductase enzymes or the development of a permeability barrier.

2-cross-resistance occurs among the nitrofurans and between nitrofuran and nitromidazole
3-chromosomal mutation to resistance develops in a gradual stepwise manner

Pharmacokinetics:

Nitrofuran is well absorbed after oral administration. Half-life is short. The drug is rapidly excreted via kidney in the urine. blood and tissue concentrations are too low for treatment of systemic infections. Urine concentrations 50-250 ug/ml. maximum excretion occurs within 3-4 hours.

N.B.: nitrofurazone and furazolidone are poorly soluble and are not absorbed after oral administration. The metabolism of nitrofuans is poorly understood because of the production of many extremely unstable metabolites in tissues.

Drug interactions:

Nitrofurans are antagonistic with nalidixic acid which act at the same site

Toxicity and side effects:

High doses of furazolidone or nitrofurantoin result in CNS effects in animals when given orally. High doses causes anorexia, nausea and vomiting in all animal species.

Lower doses in calves and dogs have caused haemorrhagic diathesis with thrombocytopenia, anemia, leukocytopenia and prolonged bleeding times. Nitrofurazone when given orally for calves at dose of 7.1 mg/kg daily is without toxic effect. Higher doses in calves when given nitrfurazone causes haemorrhagic diathesis, paralysis of limbs and with death.

Horse given po 3 times daily 8.8 mg/kg furazolidone caused anorexia on the third day. Whereas at the lower dose 4.4 mg/kg 3 times daily appeared to lose weight. In dogs given 7.5 mg/kg of furazolidone for 6 months has no adverse effects. Whereas higher doses caused dose-related neurotoxic effects

In turkeys, ducklings and chickens fed excessive amounts of furazolidone caused directly cardiotoxic effects in these species. Since nitrofurans are mutagenic and procarcinogenic, their use has been prohibited in some countries including in food animals in the United States.

Administration and dosage:

Nitrofurans are given at dosages of 10-12 mg/kg for 5-7 days to livestock. In dogs, 4 mg/kg nitrofurantoin given 3 times daily po for 5-7 days to treat urinary tract infections.

Clinical applications:

1-nitrofurans is limited use due to poor solubility and by toxicity
2-nitrofurantoin used for urinary tract and nitrofurazone or furazolidone for enteric infections in farm animals
3-local treatment of infections in the udder, uterus and skin used nitrofurans especially furazolidone

4-repeated treatment with nifuroquine of mycoplasma bovis mastitis resulted in complete disappearance of infection from a herd in which other drugs had failed. Also nifuroquine has been used successfully in the treatment of bacterial mastitis and in dry-cow mastitis.
5-the drugs used in the treatment of topical infections such as uterine infections, infectious bovine keratoconjunctivitis in cattle
6- in horse: Furazolidone, 4.4 mg/kg 3 times daily po treat salmonella diarrhea in foals. Nitrofuran used topically for treatment of bacterial infections in horses
7-in dogs and cats: nitrofurans used to treat urinary tract infections caused by otherwise resistant organisms.
8-in poultry: Nitrofurazone and furazolidone used for prevention of coccidiosis in poultry. Furaltadone used in the treatment of salmonellosis and M. gallisepticum infections. Sometimes nitrofurans used in the treatment of non specific enteritis in poultry.

Antifungal drugs

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I-Antifungal drugs for topical application

Table (1): Showing some antifungal agents for topical use

Table (1): Some antifungal agents for topical use

Drug	Antifungal activity	Drug form
Amphotericin B	Broad-spectrum, some asperigillus resistance	3 % cream
Clotrimazole	Broad-spectrum, especially asperigillus	1 % cream, solution
Cuprimyxin	Broad-spectrum, antibacterial	
Haloprogin	Dermatophytes, Candida	1 % cream, solution
Ketoconazole	Broad-spectrum	2 % cream, solution
Miconazole	Broad-spectrum, less active than ketoconazole against yeasts	2 % cream, solution
Enilconazole	Broad-spectrum, especially canine nasal asperigellosis	5 % solution
Natanycin	Broad-spectrum	2.5-5 % solution, 100 ppm spray
Nystatin	Broad-spectrum, some Candida other than C.albicans (resistant)	3.3 % solution
Tolnaftate	Dermatophytes	1 % cream, solution, powder

A-Natamycin

Natamycin is a fungicidal polyene antibiotic with action against the fungal cell membrane. Table (2) showing activity of three topical antifungal antibiotics (MIC_{90} ug/ml) against selected fungi.

Table (2): Activity of three topical antifungal antibiotics (MIC_{90} ug/ml) against selected fungi

Organism	Natamycin	Clotrimazole	Nystatin
Filamentous fungi			
Alternaria sp.	2.5	0.5-25	2-50
A. fumigatus	1.2-20	0.4	3.1-25
Fusarium sp.	1.2	3-50	6-50
Microsporum sp.	3-12	0.1-2	0.8-6.3
Mucor sp.	1.2	0.8	6.3
Trichophyton sp.	3-12	0.1-2	0.3
Yeasts			
Candida sp.	6-12	0.1-0.5	0.3-3.1
C. neoformans	5-10	1-4	0.3-1.6
Malassezia sp.	12	0.3-3	0.3

Therapeutic use:

1-application against ring worm, in the udder for yeast mastitis and on the eye for mycotic keratitis.

N.B…. Natamycin is not effective against deep mycotic infections of the eye because of poor absorption.

2-candida mastitis in cows recovered after giving 20 ml of 205 % sol. Or 10 ml of a 5 % sol., into the affected udder quarter once daily for 3 days.

3-ring worm-infected cattle treated with total body spraying with 1 L of 100 ppm of natamycin on two occasions at a 4-day interval.

4-In horses natamycin is highly effective in treating ring worm. Local sponging with 1 L of 100 ppm suspension in water on two occasions with a 4- day interval led to recovery in 4 weeks. Also, topical application in the treatment of nasal aspergillosis in horses was apparently clinically effective. Natamycin used for local treatment of candida metritis in mares.

B-Nystatin

Mode of action:

Nystatin is polyene antibiotic that disorganizes the membrane of fungi, occupying ergosterol-binding sites and altering membrane permeability so that intracellular ions leak from the cell.

Antifugal activity:

The drug is effective against candida albicans only, dermatophytes and some filamentous fungi. It is used as a topical broad-spectrum fungicidal drug.

Dosage and therapeutic uses:

For bovine mastitis–recommended dose is 300,000 units/quarteron three occasions as a single daily dose. The drug can be diluted in saline to 5000 units/ml and 50 ml administered. Nystatin has been used in dogs to treat pityrosporum infections of the outer ear. In horses to treat candida metritis.

Drug resistance:

Several candida species other than candida albicans are resistant to nystatin.

C-Azole antibiotics (clotrimazole, miconazole and elincoazole)

1-Clotrimazole

Clotrimazoleis reserved for topical application as a broad-spectrum antifungal. Used in mycotic keratitis in horse, is well tolerated, the 1 % solution is the drug of choice for aspergillus infectiona of the cornea. It is the drug of choice for yeast mastitis in cows. Intra-mammary administration of 100-200 mg/quarter/day of 1 % solution of cream, on one to four occasions as a single daily doase used in cases of mycotic mastitis in cows. It is used in the local mycotic endometritis, infusion of 400-600 clotrimazole every other day for 12 days.

2-Miconazole

Therapeutic use as clotrimazole. IV or topical administration is useful in candida mastitis in cattle. Intra-mammary or intra-arterial 50-100 mg in 60 ml of water /quarter for 8 milkings in the treatment of aspergillus mastitis. Because of toxic effect of miconazole is not the drug of choice for treatment of systemic fugal infections.

3-Eniclonazole

Eniclonazole used as an adjunct in the treatment of nasal aspergillosis in canine following surgical removal of necrotic and foreign material. In poultry houses to prevent aspergillosis using eniclonazole.

II-Antifungal drugs for systemic administration

A-Griseofulvin

Mode of action:

Griseofulvin is a fungistatic antibiotic that inhibits mitosis, probably by disorganizing the spindle microtubules. It may also interfere with cytoplasmic microtubules.

Antimicrobial activity:

All dermatophytes are inhibited by griseofulvin concentrations of 0.2-0.5 ug/ml. Other hyphal fungi, yeasts, dimorphic fungi and bacteria are unaffected. Labeled for dogs, cats, horses. Is very insoluble in water.

Pharmacokinetics:

It used orally. Absorption depends upon particle size. Microsize particles are sbsorbed twice as well. Fat feeding enhances absorption. Dosing after meals will enhances absorption. It selectively distributed to diseased skin. It is excreted unchanged via liver and bile.

Toxicity and side effects:

It may be embryotoxic, teratogenic in cats. Resistance may develop. High doses induce anemia, idiosyncratic reaction. Signs of toxicosis in cats include anorexia, vomiting, ataxia, anemia, leucopenia, anorexia, depression, jaundice, pruritus and pyrexia. Dogs and cats may vomit if given griseofulvin on an empty stomach.

Administration and dosage:

Dogs and cats: The drug given orally in the form of tablets for 3-6 weeks or longer for superficial ring worm infections and for 6-12 months for nail infections. Dose:25-50 mg/kg single dose daily. Cattle: administered as 10 % orally in the form of mycelial mix., 7.5-10 mg/kg for 7 days.

Clinical applications:

Treatment 3-6 weeks in dogs and cats. Treatment 7 days for large animals. A single large dose for prophylactic purposes. The drug is incorporated into keratin in the basal cells of the epidermis and reaches the superficial, dead, parasitized epithelium only through progressive maturation and basal cells.

B-Amphotericin B

Mechanism of action:

Amphoptericin B binds to ergosterol, the principle sterol of the fungal cell membrane, causing leakage of the cell contents.

N.B.: The antifungal effects of the antibiotic are maximal between pH 6.0 and 7.5 and ↓ at low pH. The amphotericin B sodium deoxycholate compound with phosphate buffer is more water soluble and is used for i.v. administration. The drug binds cholesterol in mammalian cell membranes less avidly.

Antimicrobial activity:

1-broad-spectrum antifungal antibiotic, it has fungicidal activity.
2-resistance…development resistance against candida sp., occur.

Pharmacokinetics:

Amphotericin B is a macrolide with lipophilic and hydrophilic parts. It is administered IV diluted as colloidal preparations. it is poorly absorbed from GIT

Toxicity and side effects:

Inhibition of kidney and liver function. Anemia. Drop in B.P. electrolyte disturbance. CNS disturbance.

Administration and dosage:

1-I/V dosage is 0.5 mg/kg 3 times a week, blood urea nitrogen (BUN) is monitored for evidence of kidney damage. On the first day the total dose is diluted in 20 ml of 5 % dextrose and 5 ml given, if no acute anaphylactic response develops in 1 minute, the remaining is given over 45 seconds. Total dose is given over minute in 20 ml of 5 % dextrose for 6-12 weeks, 3 times a week.

2-The second regimen is used in severly debilitated dogs. The initial dosage is 0.2 mg/kg i.v., increasing by 0.1 mg/kg daily until day 4 (0.5 mg/kg), then using a maintenance dosage of 0.6 mg/kg every other day as described.
3-In horse, amphotericin B has been administered every other day in daily doses varying from 0.5-1.5 mg/kg i.v., diluted in 11 of 5 % dextrose duration may extend up to 12 weeks.

Clinical application:

1-In horses amphotericin B is not suitable for the local treatment of mycotic keratitis because of its poor activity against some filamentous fungi.
2-The agent has been used successfully to treat dimorphic fungal infections in dogs, and cryptococcal infections in cats.
3-In cats, amphotericin B has been administered at a dosage of 0.1-0.5 mg/kg every 2 or 3 days in the treatment of Cryptococcus infection for 4 months.

C-Flucytosine

Flucytosine is a fluorinated pyrimidine, a low-molecular weight compound, slightly soluble in water but readily soluble in alcohol.

Mode of action:

After permease-mediated entry into the fungal cell, flucytosine is deaminated to 5-fluorouracil, which is incorporated into messenger RNA. This perverted mRNA functions poorly, garbing condon sequences and producing faulty proteins.

Antimicrobial activity:

Flucytosine has a narrow spectrum of antifungal activity. It is active against most C. neoformans, 80-90 % of candida and cladosporium and few asperigillus strains. The majority of yeast isolates from bovine mastitis are resistant also dermatophytes other filamentous fungi and dimorphic fungi are resistant. MIC $\leq$ 16 ug/ml is susceptible, the drug is fungicidal at concentrations five times MIC.

Resistance:

1-About 10-20 %, 1-2 % of candida and C. neoformans, respectively show resistance for the drug (primary resistance).
2-Developed resistance occurred in vivo and in vitro against two-thirds of fungal isolates during treatment.
3-Combination with amphotericin B is commonly used synergistically because amphotericin B increases fungal permeability to flucytosine.

Clinical application:

1-it is used in treatment of cryptococcuas infection in cats. Given over 4-9 weeks.
2-addition to amphotericin B to prevent the emergence of resistant mutants.

Antituberculosis

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I-Rifampin

Rifampin: is the synthetically antibiotic products of streptomyces mediterranii. Rifampin is a hihgiy active first-line oral drug for the treatment of tuberculosis in humans. It is always combined with other antibiotics because of the ready development of resistance to the drug. It has good activity against G+ve bacteria and anaerobic and some antiviral and antifungal activity.

Mode of action:

Rifampin has the unique action among antibiotics of inhibiting RNA polymerase, the enzyme that catalyzes the transcription of DNA to RNA . Rifampin binds to the beta subunit of the enzyme and causes abortive initiation of RNA synthesis. G-ve bacteria are relatively impermeable to the drug.

Antimicrobial activity:

Rifampin is a bactericidal antibiotic with a wide spectrum of antimicrobial activity. It is inhibitory to bacteria, Chlamydia, rickettsia, some protozoa, some fungi and pox viruses. It is particularly active against G+ve bacteria and some mycobacteria mainly mycobacterium tuberculosis.

Resistance: Chromosomal mutation to high level resistance develops readily in most bacteria. Some mutants show stable changes in RNA polymerase that prevent binding. Because the mutation rate is so high. Resistance is not transferable and there is no cross-resistance with other antibiotics.

Pharmacokinetics:

Absorption is a good after oral administration in monogastric animals and peak blood concentration occur within 2-4 hours. The half-life in horses 6 hours, in calves 3 hours, in sheep 4.5 hours, in dogs 8 hours. The drug is highly lipophilic and diffuses rapidly into tissues reaching concentrations exceeding those in serum. Penetration phagocytic cells is excellent, achieving several times those of serum. Penetration into CSF is poor but is improved by inflammation (10-90 % of serum concentrations). After intestinal absorption, rifampin is net absorbed in the liver largely to 25 desacetylrifampin, bioactive form. Peak serum concentration 40 ug/ml in dogs, 2.9 ug/ml in horses, metabolism in foals is lower than in adult horses, 1 ug/ml in adult sheep for about 8 hours following oral dosage with 10 mg/kg. Excretion of rifampin partially in bile and partially in urine so rifampin metabolites may color urine, saliva and feces orange red.

Drug interactions:

1-Concurrent use with other antibiotics reduces the development of mutants resistant to rifampin, which should generally not be used alone.

2-Drug interaction may be synergism or antagonism in vitro studies. e.g… the interaction of rifampin with cloxacillin in the treatment of experimental S. aureus endocarditis both antagonism and synergism were observed depending on the dosage.

3-Rifampin showed synergism with erythromycin and penicillin G against R.equi in vitro but was antagonistic with gentamicin.

4-Synergism with amphotericin B has in fungal infection.
5-Rifampin is a potent hepatic enzyme inducer & produces clinically important increases in the rate of metabolism of other drugs including oral anticoagulants, digitoxin, barbiturates, theophyllin, ketoconazole, corticosteroids.

Toxicity and adverse effects:

The drug may be teratogenic and should not be administered to pregnant animals. Hepatotoxicity of varying degree occur so it should not be administered to patient with liver disease e. g… in dogs, increases in hepatic enzyme activities may be relatively common and progress to clinical hepatitis, which may be fatal in dogs with history of liver disease.

Administration and dosage:

Horse (po 5 mg/kg capsules), dogs (po mg/kg capsules), sheep and calves (20 mg/kg po in capsule form) and adult ruminants (i.m. or i.v. injection 10 mg/kg).

Clinical application:

1-In Vet. Use: Rifampin used against macrophage-associated bacteria such as brucella, R. equi and intracellular S. aureus in bovine mastitis.
2-With erythromycin used in the treatment of R. equi pneumonia in foals.
3-Combination of streptomycin-isoniazidirifampin used in the treatment of jhon's disease in goats.

II-Fusidic acid

Fusidic acid is a lipophilic steroid antibiotic. It is a product of fusidium coccineum and available as a readily soluble sodium salts.

Mode of action: It prevents protein synthesis by inhibiting the binding of aminoacyl tRNA to the ribosomal A site.

Antimicrobial activity:

a-sodium fusidate is active against G+ve bacteria. It is a bactericidal activity against S. aureus and M. tuberculosis.
b-G-ve bacteria rods resistant.
c-combination with penicillin prevents the emergence of the mutants resistant.

III-Isoniazid

Isoniazide is the hydrazide of isonicotinic acid, low molecular-weight. Water soluble drug. It is a bactericidal to M.tuberculosis at concentrations of 0.05-0.2 ug/ml of mycobacterium bovis. Mycobacterium ovium intracellular and other atypical mycobacteria are resistant. The drug is never administered alone because resistant bacteria develop readily. The drug is well absorbed from the intestine and distributes well into the tissues, including CSF.

Toxic effects:

Administration of 11-22 mg/kg to a cow orally for 28 days produced no ill effects. Higher doses caused anorexia and depression. Accidental ingestion of 66 mg/kg by dog bed rapidly to convulsions treated by barbiturates. Mycobacterium paratuberculosis is moderately susceptibe to isoniazid, 2 ug/ml. Combination with rifampin or use of isoniazide alone in paratuberculosis in goats has been unsuccessful. Isoniazide has been used with moderate success in the prevention and treatment of M. bovis infection in cattle in south Africa.

Anti-parasitic drugs

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The parasite problem in animals is one of the health and economics.

Parasitic disease: the parasites are causing pathophysiological changes that are manifested in clinical disease.

Patho-physiology caused by internal parasites:

Diarrhea. Anemia. Tissue insult from larval migration, predisposes the animal pneumonia, enteritis, intestinal rupture, cirrhosis and liver abscess. Aneurysm and embolism. Animal is more susceptible to viral and bacterial invasion. Animals are unthrifty, do poorly. Decreased productivity such as decreased weight gain and feed efficiency, decreased carcass value, decreased milk production.

Patho-physiology caused by external parasites:

Skin irritation, loss of hair, sunburn and infection. Upset of animal's nervous system. Loss of blood and fluids and anemia. Decreased productivity such as decreased weight gain and feed efficiency, decreased hide and carcass value, decreased milk and wool production. there are also insect vectors that may transmit diseases.

General summary for parasitic control measures:

Good management and husbandry and sanitation. Natural immunity. Acquired immunity. Anti-parasitic drugs

Judgments relative to the use of anti-parasitic drugs:

1-efficacy: spectrum and efficacy…..against mature or immature forms and/or inactive forms. Also timing….use when efficacy is maximum

2-safety: if there is adverse effect of drugs. Might there be any drug interaction.

3-must figure out if treatment is economically sound: drug costs-economic benefit or gain to animal-cost of handling the animals, man hours-compatibility with simultaneous procedures-weight benefit vs risk.

Precautions with anti-parasitic drugs:

1-all are potentially toxic, direct toxic action of the drug on the animal, secondary pathology

2-follow label directions…dose, route of administration, precautions.

3-use care with young, old and debilitated animals.

4-don't use in pregnant animals unless so labeled

5-know whether they absorbed into the systemic circulation or not if given orally or applied to skin.

6-know how they are excreted and/or inactivated if they become systemic

7-must know if there are any contraindications due to idiosyncratic adverse reactions in a particular species or breed.

Summary of general toxic anti-parasitic drug reactions:

1-Local irritations: to the pharynx, larynx, stomach, intestine or skin. Difficult breathing due to swelling of air passages. Emesis. Diarrhea. Perforation of intestinal wall.

2-Systemic: must be absorbed and reached to the blood to be toxic. Organ toxic reactions as liver, kidney, CVS, Respiratory S., CNS and ANS. Drug interactions. Actions not intended.

Secondary pathology that may be brought about by anti-parasitic drugs:

1-usually result from the ideal effects of drug that is circulating systemically.

2-Pathology that is due to dead or dying parasites:

Cause mechanical blockage of the blood vessels. Cause an inflammatory response of tissue surrounding the dead or dying parasites. Bring about a shock-like syndrome. Killing of microfilariae of Onchocerca species when using ivermectin in horses can cause pruritis, ventral abdominal edema, limb edema, eyelid edema and fever.

Anthelmintics

Definition:

These are drugs which either kill or remove parasitic worms infesting mainly the digestive tract and associated organs. They are also termed vermicides which kill the worm end vermicides which expel the worm but do not kill it. Helminthiasis in animals has a great economic importance in the whole world. The economic losses in the body weight and gain in farm animals and because of the risk of transmission of the parasites to humans, encourage the risk of transmission of the parasites to humans, encourage the control of these parasites.

Properties of ideal anthelmintic:

It must be non toxic to the host and highly effective on the worms. It has a wide therapeutic index. It has low cost. Easy to be administered.

Anthelmintic resistance:

Resistance and cross resistance occurs among anthelmintics. The resistance transmitted on genes through eggs of helminthes. The resistance when carried on one gene occurs rapidly as in thiabendazole and slowly on morantel, which due to that carried on a number of genes.

N.B

1-Changes of anthelmintic may lead to confusion and difficulty in diagnosis, so do not change it or change the anthelmintic program suddenly.

2-Use one anthelmintic as long as it remains effective.

3-Better to use broad spectrum anthelmintics removing all worms from the host as possible.

General mode of action of anthelmintics:

1-Influencing nerve transmission in the parasites leading to paralyzing the neuromuscular system of the worm losing their attachment to the gut wall.

2-Inhibiting the enzyme system of the worm e.g inhibiting the fumerate reductase enzyme which is vital for energy metabolism, so there are interference with parasitic development and energy metabolism for both larval or adult stages.

3-Penetrating or dissolving the cuticle of the worm.

4-Necrosis of the worm.

Classification of anthelmintics:

According to their effect on different kinds of worms on (or clinical application) the digestive tract into:-

1-Drugs used against nematodes (round worms)…..called anti-nematodal drugs (Nematocides).

2-Drugs used against cestodes (tape worms)…..called anti-cestodal drugs.

3-Drugs used against trematodes (flat worms)……called anti-trematodal drugs or anthelmintics for flukes (Fasciolicides).

Drugs acting on Round worms
(Anti-nematodal drugs)

These are drugs which are used for treatment of animals infested by nematodes (round worms) such as: Ascaris, Strongylus and trichostrongylus. The worms collect forming a ball mass, so they cause intestinal obstruction.

They are classified into:-

I-Old anthelmintics: Mixture of nicotine and copper sulphate.

II-Plant origin

a-Santonium---santonin (from plant Artemesia cina)

Action:----Santonin directly stimulates the parasite musculature causing active movement which detach the parasites hold and can be expelled by purgative which should be given 3 hours after administration.

Dose:-----previous starvation is inadvisable as it favors absorption of santonin. Give mercurous chloride, by its purgative action assists in the removal of worms and also reduces the absorption of santonin from the small intestine. It is chiefly used against large round worms in horses, pigs, dogs and cats. In cats usually given in small doses on 4 successive days.

Toxicity of santonin in dogs:----twitching of muscles of the head, temporarily blindness, grinding of teeth, colonic spasm, convulsions, irregular and unsufficient respiration and finally death from asphyxia.

b-Oleum chenopodii:---- chenopodium oil -American worm seed oil

It is an oil distilled from fresh flowering and fruiting plants of chenopodium ambrosidioides. It contains not less than 65 % of ascaridole with terpenes which give it the characteristic unpleasant odor.

Dose: Horse dr. 2----dogs Min. 2-10----puppies Min. 0.5-2

Action and uses:

Chenopodium oil is an anthelmintic used in the treatment of round worms in horses. Its anthelmintic effect depends on its ascaridole content. It should be given after a preliminary period of fasting with an oil purgatives; in case of horses linseed oil is preferred. Purgation is especially important since the drug inhibits peristalsis and also because of the toxic effects of the drug on the liver. No food should be given until the purgative has acted. It may be found necessary to repeat the treatment in a week to ten days to expel any worms that may have escaped the first treatment.

Toxicity:

GIT irritation, vomiting, dyspnea and death. In case of toxicity saline purgative should be given and the animal should be kept worm.

Contraindications: It is contraindicated in the following cases:

pregnant mares, very young animals, old or debilitated animals, It should not be given to cats as they show low tolerance to it .

c-Oleum terebinthinae:----Oil of turpentine

It is a volatile oil distilled from the oleo-resin (turpentine) obtained from various species of pinus.

Doses: Horses oz 1-2-------cattle oz 2-4------dogs Min. 2-20

Action and uses: Externally turpentine is a counter-irritant and used as liniment by itself or other drugs in rheumatic pains of joints and muscles and for sprain tendons. Internally oil of turpentine possesses anthelmintic effect for round worms in animals. (a, b and c are replaced by phenothiazine).

III-Recent anti-nematodal drugs

Are classified according to their chemical structures into:

Benzimidazoles, Imidathiazoles, Tetrahydropyrimidines, Organophosphorous compounds, Piperazines, Avermectines

IV-Chemically unreiated antheimintics

A-Benzimidazoles

Action: Anthelmintic

Mode of action: They act by conversion inside the cell into methyl-benzimidazole which cause degenerative changes in the intestinal cells in the parasitic nematodes by interaction with cytoplasmic microtubules.

Side effects: They has teratogenic effect so contraindicated for pregnant animals. Residues for up to one week after dosing are recorded.

1-Thiabendazole(Thiabenzole)

Action and mode of action: It is very effective anthelmintic, larvicidal acting by inhibiting egg production. It has no residual action and better given continuously or in repeated doses every 6 weeks in spring and summer.

Side effects: It prevents the development of immunity. It has teratogenic effect.

Pharmacokinetics: Given orally and absorbed from rumen and GIT.

Metabolized in liver as glucuronides and sulphates. It is excreted in the urine and faeces.

Dose: 50-100 mg/kg (cattle and horses).

Toxicity: Resulted from large doses. Symptoms are anorexia, salivation, depression and liver and kidney damage.

2-Parbendazole (Helmotac)

Similar to thiabendazole. Used for nematodes in sheep and cattle giving in food. It has a teratogenic effect.

3-Cambedazole

Similar to thiabenzole effective in nematodes in horse, sheep and cattle. It has teratogenic effect.

4-Phenbendazole (Panacur)

Effective against nematodes (GIT and bronchi) in sheep, goats and calves. Also it is used in horses, cattle, dogs and cats.

5-Mebendazole (Telmin)

Similar to thiabendazole but it is safe for pregnant animals and used in dogs and poultry.

6-Thiophanate

Similar to thiabendazole but it may cause liver and kidney damage.

7-Albendazole

Anthelmintic for cattle and sheep. Contraindicated in pregnant animals due to teratogenic effect.

8-Oxibendazole

Anthelmintic for lung worms in cattle and sheep. It has teratogenic effect.

9-Febantel

Anthelmintic used for horses, cattle and sheep GI and lung worms.

10-Oxfendazole

As febantel, it is a teratogenic.

B-lmldazothiazoles

Includes tetramisole and levamisole. Single dose is effective orally or parentrally.

1-Tetramisole

Mode of action: Acts by depolarizing effect leading to spastic paralysis of worm.

2-Levamisole (Citarin)

It is the L-isomer of tetramisole. It acts against nematodes of GIT and bronchi for domestic animals and birds.

Side effects: It has a neuromuscular blocking effect on the host tissues. It is contraindicated in horses and better not used in sheep with liver damage treated with carbon tetrachloride.

Dose: Cattle 7.5 mg/kg orally or 2 ml (18.2 %) per 50 kg.

Toxicity: Depression, salivation, deification, colic and muscular tremors are sometimes observed.

C-Tetrahydropyrimidines

These are derivatives of imidazothiazole including pyrantel and morantel. They have a broad spectrum anthelmintic activity.

1-Pyrantel tartarate (Strongid)

It is a non toxic anthelmintic used for pregnant animals against nematodes.

Mode of action: It act by paralyzing the worm muscles by depolarizing action. It has a local anesthetic effect and nicotine-like action.

Dose: Cattle 28 ml (5.9 %)/kg. Horse 11mg/kg.

2-Morantel tartarate (Baniminth)

Similar to pyrantel tartarate. It is used as bolus for slow release in the rumen.

D-Organophosphorous antheimintics

Mode of action: They act by forming stable compounds with cholinesterase of nematodes.

Side effects: They cause only slight depression of the host cholinesterase.

1-Haloxone (Loxon)

The drug act against adult nematodes of sheep, cattle, horses and carnivorous beside its effect as larvicidal action. It is used with food.

Dose: For cattle------35-50 mg/kg.

Toxicity: Toxicity resulted from very large dose (10 times) the therapeutic forms. Symptoms are anorexia, diarrhea and death in several days. Treatment of toxicity by atropine and 2-PAM.

2-Dichlorvos

3-Caumaphos

4-Trichlorphon

All (2,3 and 4) are effective against nematodes in horses and dogs.

5-Metriphonate (Neguvon-Deptrix)

It is used for the warble fly externally and internally as a drench for nematode infestation in cattle.

Side effects: It is not used in sheep or goats as nearly toxic due to inhibition of cholinesterase but recovery occurs in few hours.

Dose: Cattle-------55 mg/kg.

E-Piperazine (Coopane-Antepar-Oxacine)

Piperazine given by mouth (tablets, capsules as a drench or in food in the form of adipate, citrate, hydrate phosphate or as a complex with carbon disulphide). Readily absorbed and metabolized and 40 % excreted in urine.

Mode of action: It has a curare-like effect on the parasite muscle wall antagonizing A.ch. leading to paralysis and by peristalsis leads to expel of the parasite. The repeated dose is necessary for the larvae in the tissue is not affected.

Dose: 0.11mg/kg.

Diethylcarbamazine acid citrate (Banocide):

It is a piperazine derivative active against microfilaria. It is given by mouth in gelatin capsules. It is given for calves and sheep against round worms of bronchi.

Dose: 30 mg/kg Three times daily for 3-5 weeks.

F-Avermectines

Action and node of action:

Ivermectin paralysis nematodes and arthropods by stimulating GABA mediated chloride ions conductance and it has significant competitive neuromescelar blocking activity. Ivermectin is used for the treatment and control of GIT nematodes, warbles, lung worms, mange and suckling lice in beef and non lactating dairy cattle. It is given orally or s/C injection or the form of paste. Its withdrawal time is 21 days before slaughtering of cattle and should not be used in milking cows or in dry cows 28 days before calving.

Toxicity: In large dose it causes paralysis.

Dose: Ivomec oral----------0.08 % 2.5 ml/10 kg b.wt.
Ivomec inj.----------1 % 1ml/50 kg b.wt. S/C
Eqvalan----------20 % inj. 1 ml/100 kg b.wt.
Eqvalan paste----------0.2 gm/kg b.wt.

IV-Chemically unrelated anthelmintics

1-Phenothiazine (Phenovis)

It is used against nematodes of sheep, horses and cattle. It is green yellow powder which colors the urine and milk red.

Mode of action: Act by inhibiting glycolysis and the egg-laying of worms.

It is given by mouth as tablets or suspended in water. It is given in small continuous doses to reduce the larvae on a pasture. It is given in combination with piperazine in horses to reduce the risk of toxicity.

Doses: Cattle----------20-60 mg (10 %) 50 kg.

Horses---------10-30 gm (3 %) 150 kg.

Toxicity:

In horse-------haemoglobinurea and jaundice.

In calves-----photosensitization due to the accumulation of sulphoxide which is photodynamic agent resulting in keratitis and corneal ulceration.

2-Bephinium hydroxynaphthoate (Alcopar)

It is a safe used for nematodes. Given by drench.

3-Thenium closylate (Ancaris)

It is given with piperazine to dogs infested with nematodes.

Toxicity: Vomiting, diarrhea and muscular weakness.

Anthelmintics for tape worms

I-Plant source

1-Filix mas-male fern

Active principle (Filmarine):

It decomposes into filicic acid and aspidinol.

Preparation: Liq. Ext. male fern 24-26 % of filicin

Dose: Horses and cattle-----oz 0.5-1.5. Dog----Min 15-20

Action and uses:

Extract of male fern is used in the treatment of taeniasis. It is poisonous to all varieties of tape worms. In dogs the extracts should be preceded and followed by a saline purgative at intervals of 12 and 6 hours respectively. Also in dog oleogenous purgatives such as castor oil should be avoided during treatment as they may dissolve the filicic acid and facilitates absorption and the production of toxic effects. The drug given in capsules for dogs. In sheep given in oil and repeated daily for three days. The drug destroys the parasites which then disintegrate and are expelled from the bile ducts

Contraindications: In cases of anemia, pregnancy, febrile conditions and in very young or very old animals. It should not be given to cats as they are particularly susceptible to its toxic action.

2-Pelletierine tannate

It is a mixture of the tannates of the alkaloids obtained from the bark of the stem and root of punia granatum (the pomegranate).

Action and uses:

Pelletierine has little action on round worms, but is a powerful taenicide. The tannate is used because it is insoluble in the stomach and in the intestine the alkaline secretions liberate the free alkaloids. It is usually given to the

fasting dog in doses of 4 grains suspended in water and this is followed by a purgative (castor oil) in an hour or two.
Dose: Dogs-------gr. 4

3-Kamala

Source: It is a reddish powder consists of the minute glands and hairs obtained from the surface of the fruits of Mallotus philippinesis. It contains rottlerine, resins and wax.
Doses: Dogs--------gr. 30-dr. 2. Cats---------gr. 10-15
Action and uses:

It has general anthelmintic and purgative actions. It is used for eradication of the tape-worms in cats and dogs. It is usually given mixed with syrup, given in capsules or mixed with milk. It is also used in the treatment of tape-worms in poultry in doses gr. 8-20

4-Atebrin-Mepacrine HCl

Atebrin has antimalarial and anticoccidial effect in poultry. It has recently an anthelmintic effect against taenia in poultry. The dose was preceded and followed by a purgative. It stimulate the parasite musculature causing active movement not kill the parasite.

5-Arecholine

Source: It is an alkaloid obtained from areca nuts. It affect mainly tape worms in dogs. It is a parasympathomimetic drug.
Action and uses:

It act by relaxing the muscle of taenia so that they loose their attachment on the intestinal mucosa of the host. It also stimulate the intestinal movement of the host and so it can expel the detached worms. Treatment may be needed to be repeated 2-3 times at 7-10 days intervals.
Nemarol----is a patent preparation which contains arecholine and acetrasol which is effective anticestodal drugs for dogs.

II-Synthetic source

1-Dichlorphen (Teniathane)

Action and uses:

It is used to treat dogs and cats affected with tape worms. It results in the detachment of the tape worms in 30-40 minutes after dosing. Worms then disintegrate in the gut and no segments are passed with the faces. No need for withholding food before administration and it does not cause severe purgation as arecholine.
Side effects: It may result in vomiting, colic and diarrhea.
N.B Its dose is very bulky which make its administration difficult.
Dose: 0.3 gm/kg.

2-Bunamidine HCl (Scoloban)

It is effective against cestodes in cats, sheep and chickens.
Side effects: Vomiting, diarrhea and death in dogs may occur from ventricular fibrillation as it sensitizes the heart to catecholamine.

3-Niclosamide (Mansonil-Yomesan)

Action and uses: It acts by paralyzing tape worms. It is effective against T. pisiformis in dogs and t. taeniformis in cats, Moniezia in sheep and Riallietina species in birds. No toxicity is recorded.

Dose: One tablet (500 mg) /3kg.

4-Dicarbodine

A recent drug with high effect against tape worms in dogs.

Drugs acting on flukes or trematodes

It is grouped into old and new fasciolicides.

I-Old fasciollcides

1-Carbon tetrachloride

It is clear, colorless, heavy volatile liquid with characteristic odor and a burning taste. It is insoluble in water but miscible with alcohol.

Action and uses: Carbon tetrachloride is an anthelmintic and is used chiefly Against liver flukes in sheep and sometimes in cattle. It kill the mature flukes and causes their expulsion from the gut. Immature flukes are relatively resistant so that it may be necessary to repeat the dose at monthly intervals. In heavily infested places monthly doses from autumn to spring are advisable. It is given to dogs in a single dose after 12-16 hours fasting and may followed by saline but not any oily purgative.

Dose: Sheep 1-3 ml in gelatin capsules or as a drench mixed in 300-600 ml of liquid paraffin. Sheep can be injected 3ml (50 % solution).

Toxicity: The toxic symptoms observed in dogs are loss of appetite, lack of energy and titanic spasms followed by coma. Toxic effects of carbontetrachloride are commonly aggravated by: debility, feeding high protein ration as oil cakes, calcium deficiency, pregnancy and lactation. Toxicity appeared in the livers as fatty changes is due to the block of secretion of triglycerides by the hepatic cells which thus accumulate in the cells. Hypocalcemia may be due to the accumulation of calcium in the liver.

Treatment of toxicity: by giving calcium borogluconate

2-Tetrachlorethylene (C_2Cl_4)

It is more volatile than carbontetrachloride and less toxic. It is used for treating abomasums worms in ruminants. Copper sulfate 2 % solution is given before its administration to close the esophageal groove in order to let the drug goes directly to abomasums. It is given in capsules or by stomach tubes after fasting 24 hours followed by a saline purgative. The toxicity ot tetrachloethylene is lower than that of carbontetrachloride and in normal therapeutic doses it is unlikely to cause liver damage. In dogs treatment may consists in giving 3,4 and 5 doses at hourly intervals on 3 successive days and 3 hours after the final dose, purgative is given.

3-Hexachloroethane (HCE; Avolthane)

Pharmacokinetics: slowly absorbed & slowly excreted in expired air, bile and urine. its metabolites are tetrachlorethylene and pentachloroethane in sheep.

Side effects: It causes liver damage in therapeutic doses. loss of appetite and diarrhea.
Toxicity: high protein diet may be predisposing factor for toxicity
Treatment: Give calcium borogluconate
Dose: cattle (15-100 gm) and sheep (8-15 gm).

II-New fasciolicides

1-Hexachlorophane (Fascol, Coopaphane)

Action and uses: it is fasciolicide given sc injection or orally in oil or aqueous suspension or in propylene glycol.
Side effects: it may cause death due to biliary occlusion
N.B…it has the advantage of not tainting the flesh or milk whereas hexachloroethane taint the milk

2-Oxyclozamide (Zanil)

Action and uses: A recent fasciolicide acting by uncoupling oxidative phosphorylation.
Dose: cattle (10 mg/kg) and sheep (10-20 mg/kg)

3-Tribromosalan (Hilomid)

A fasciolicide used in sheep given as drench. It has an effect on immature flukes.
Dose: sheep…30 mg/kg for mature flukes and 60 for immature flukes.

4-Nitroxynil (DovenEx)

Action and mode of action: A fasciolide drug acting by uncoupling oxidative phosphorylation. It acts mainly on mature flukes. It is given sc or im injection.
Side effects: ↑ B.P., respiration and body temperature. Deaths occurs in sheep.
Dose: sheep and cattle…10 mg/kg (20 % solution)

5-Niclofolan (Bilevon R, Bilevon M and Bilevon inj.)

Used for cattle. Its effect is similar to dovenex.

6-Rafoxanide (Ranide)

Action and uses:
it is a fascilicide mainly effective in cattle against 98 % mature flukes and 50 % of the immature parasites. The dose repeated after 3-6 weeks
Dose: cattle and sheep……10 mg/kg.

7-Tricalbendazole (Fasinex)

It acts against early immature, immature and adult worms. It is safe and could be used for pregnant animals that it had no teratogenic effect.
Dose: 10 mg/kg b.wt. orally in tablets or suspension or parentrally.

Molluscicides

The control of fascioliasis usually involves molluscicides to eliminate the snail intermediate host by: copper sulphate (at conc. 25 kg/hectare) and sodium pentachlorophenate (10 kg/hectare).

Antiprotozoal drug

Parasitic protozoa are responsible for several diseases in man and animals. They are frequently transmitted by blood sucking insects. They may be tissue parasites (coccidiosis and Entamaebia) or blood parasite (babesia, Thieleria, anaplasma and trypanoma). So it is necessary to study the chemotherapeutic agents used in treatment of protozoal diseases in different animal species and birds to improve productivity.

I-Anticoccidial drugs

These are drugs used for treatment of coccidiosis in animals or poultry , they may be coccidiostatics or coccidiocidal. Anticoccidials may act on extracellular stages (sporozoitesmerozoites) to prevent pentration of cells or on intracellular stages to inhibit development, few act on sporulation of the oocyst. The major problem is the development of drug resistance against anticoccidials the speed of development of this resistance depend on the mechanism of action of the drug , also cross resistance occur to drugs with same mode of action . Resistance is slowly appear with ionophores and rapid with quinolones. Drugs combinations decrease drug resistance. Ideal anticoccidical drug must be cheep, broad spectrum and leaving no residues in the carcass.

Anticoccidials include the following groups:

1-Sulphonamides

Were the first effective anticoccidalsused . But because of drug resistances and development of new broad spectrum anticoccidialssulphonamides are infrequently used in modern poultry production, However still of value in upper intestinal tract chicken infection. They still widely used in treatment of coccidiosis of ruminants and small animals.

Mode of action: Compete with PABA essential for folic acid synthesis resulting in destruction of schizontscontaingmerozoites.

Coccidiosis may be intestinal or hepatic.

a-Intestinalcoccidiosis: in poultry and mammals treated with Sulphaguanid-ine, sulphaquinoxaline, Sulphamethizine, sulphadimidine and sulphamerazine.

b-Hepaticcoccidiosis : treated with systemic sulphonamides either by IM injection or in food and drinking water.

a-Sulphaquinoxaline used as 0.01 % prophylactic and 0.04- 0.05 % for treatment.

b-Sulphadimethoxine&sulphachloropynazine are more effective than other sulphonamids user 0.5 1.5 % in food.
c-Sulphamethezine used 5 mg/kg ration
Sulphadimidine used as 16 % solution added as 0.2 % in the drinking water or as 33 % solution to be injected in hepatic coccidiosis.
d-Sulphaguandine used 0.5-1.5 % in food.
e-Sulphonamide combination decrease the occurrence of resistance and increase efficacy:
i-ormetoprism and sulphadimethoxine
(68.1 gm and 11.35 g/ton ration)
ii-pyrimethaminewith sulphaquinoxalione
iii-pyrimethamine with sulphadoxine (25mg and 500mg)

2-Nitrofurans

Including nitrofurazone, furazolidone, furaltadone metronidazole, Dimet-ridazole and acinitrazole were used for treatment and prevention of coccidiosis but become of limited value because of potential carcingenci activity.

3-Dinitro Compounds:

a-Nicarbazin (Nicarb): It is used as prophylactic only for coccidiosis in broilers at dose of 125 ppm in food especially in starting period because of potential growth suppression. It is not used in layers as it may reduce egg production, decrease hatchability, thin egg shell and mottled egg yolk.
b-Dinitrolomide: Used as prophylactic at dose of 0.0125 % in food by inhibiting sporulation of the oocyst.

4-Vitamin antagonists

a-Amprolium hydrochloride: It is safe coccidaostatic agent, competitively inhibits the active transport of thiamine. It affects first generation shizont to prevent production of merozoites, some activity on sexual stage and sporulatingoocyst. It is given in food 36.3 113.5 g/ton or 0.012 % in drinking water and may be combined with sulphonamides as sulphaquinoxaline or sulphadimidine it can be used safely in laying hens.
b-Diaverdine: It is coccidiostatic drug, antagonizing folic acid essential for Eimeria and is given (0.001 %) combined sulphquinoxaline (0.008 %). It has low toxicity.
c-Ethopabate: It antagonizes PABA needed for folic acid synthesis. It can be used with diaverdine or pyrimethamine.
d-pyremethamine: It is folic. folinic acid antagonist given with diaverdine or sulphoquino-xaline to potentiaateanticoccidial activity.

5-Hydroxy and naphtha quinines

a-Buquinolate: It is coccidiostatic allow penetration of sporozoties but not development, active against all species of coccidia in chicken added at 80 ppm in food.

b-Clopidol: It resembles bequinolate used as 0.01 % in food, However there is cross resistance to bequinolate it need 5 days withdrawal period.
c-Decoquinate: It is the most active one and more safe . it is not used in laying or breeding birds and needs 5 days withdrawal period from meat.

7-Robenidine (Cycostat)

It acts on first generation schizont preventing formation of merozoites but causes unpleasant taste of meat and egg and needs 5 days withdrawal period. It is used against ionophores resistant strains in feed at rate of 33 ppm.

8-Ionophores

A group of broad spectrum coccidiostatic antibiotics. They act by interfering with cellular ion transport accumulating Na and Cl intracellular. They act on extraceullarsporozoites. They include:
a-Monensin (Coban): Is produced from streptomycescinnamonensis. It is effective for prophylaxis of coccidiosis in broilers fed at 99-121 ppm. It may cause weight gain supperession.
b-lasalocial (Avatec): It is related to monensin but of greater activity and toxicity lasalocid is transm-itted to egg and also may cause wet litter. Given at rate of 75.125 ppm in feed
c-Salinomycin (cox): It is used for prevention of coccidiosis in broilers feed at 6 ppm, affecting sporozoites, early and late asexual stage and must not used in layers.
d-Naracin sodium (Monteban): It is used for prevention of coccidiosis in broilers given in feed 70 ppm.

9-A prinocid (Arpocox)

An anticoccidial act by inhibiting nucleic acid synthesis. It is rapidly metabolized used 60 ppm for prophylaxis with no adverse effect.

10-Toltrazuril (Baycox)

It is a broad spectrum anticoccidial, affects all stages of Eimeria. Given in drinking water 25 ppm it needs 19 days withdrawal period as it is slowly removed from meat.

II-Antimaebic drugs

These are used for treatment of amaebic dysentery and they include:

1-Emetine

It is alkaloid obtained from ipecac (Brazil root) or prepared synthetically. Emetine is direct acting systemic amacebicid, administrated parentally because. When given orally erratically absorbed. It acts mainly on the trophozoites slowly eliminated from body via kidney with trace amounts detected in urine 1-2 months after the end of the therapy. It is especially of value in sever invasive intestinal amaebias, amebic hepatitis, amebic abscess.

Dose: mg/kg B.wt with 60 mg/day maximum dose. For a period not more than 10 days. It is contraindicated in cardiac renal disease hypotension & pregnancy.
Side effects: Nausea, vomiting, diarrhea, tenderness and stiffness of muscles, cardiac depression
Derivatives of emetin:
a-Dehydro emetine: less toxic and cummlative than emetine (1.5 mg/kg not exceed 90 mg/day) IM
b-Emetine bismuth iodode: it is given orally 200 mg/day orally for 12 day.

2-Halogenated 8-hydexyquinolines

These are iodinated compounds include: chinioform (yatran), iodocholor-ohydroxyquin (viofofm), Diiodohydroxyquin (Diodoquen). It is only effective for intestinal amaebiasis acting on the trophozoites.
Side effects: Neurotoxicity, optic atrophy and visual loss may improve after discontinuation.
Dose: Chinioform (0.75-1 gm/day for to days), vioform (0.75-1 gm/day for to days), Diodoquin (1.5-2 gm/day for 3 weeks)

3-Metronidazole (Flagyl)

It is very effectively eradicates amebic tissue infections (liver abscess, intestinal wall and extraintestinalinfection) . It has Short half life must repeated every 8 hours.
Mode of action: occur in 4 steps: 1-entry to protozoal cell. 2-Reductive activation 3-Toxic effects of reduced products 4-Release of inactive end products.
Side effects: Glossitis, stomatits, nausea, emesis and in high dose nervous signs and suspected as mutogene and carcinogens
Use and dose: E. histyhtica in dog orally 15-30 mg/kg. b.wt and it is used for treatment of in cat 10.25 mg/kg twice for daily 5-7 days.

4-Chloroquine phosphate

It is antimalarial with special therapeutic value in amaebicheapatitis as it localized in liver in concentration several hundred times greater than that of plasma. It is given orally at a dose of 1 g daily for two days then 500 mg/day for 2 or 3 weeks. It is of low toxicity and the dose may increased and duration prolonged if needed.

5-Pentavalent organic arsenicals

Carbarsone and Glycobiarsol effective against amaebic hepatitis by interfering with SH group containing enzyme in the parasite. carbarsone

readily absorped from GIT and slowly excreted by kidney while Glycobiarsol is poorly absorbed and exerts its effect on intestine
Dose: of carbarsone 250 mg tid for 10 days and for Glycobiarsol 500 mg tid for 10 days. It is contraindicated in renal and hepatic diseases

6-Antibiotics

a-paromomycinamiroglycoside antibiotic: it has direct amaebicidal activity in mild and moderate amaebicine. Dose 25 mg/kg b.wt orally for 5 days. Side effects mild GIT upsets, mal-absorption diarrhea .
b-Fumagillin as paromomycin: given at a dose of 10-20 mg TiD for 10 days
c-Tetracycline: has very week direct amaebicidal action may eradicate intestinal amaebiasis but not used in pregnant or young animals .

III-Antipiroplasmal drugs (Babesiocidal)

These are drugs used for treatment of babesia infection in animals and they include the following.

1-Trypan blue

Is one of azo dyes and considered as treatment for babesiasis it is safe nontoxic but stains tissues, secretions and milk with blue green color persist for several weeks .

2-Quinuronium suphate (Acaprine)

It is a complex urea compound affecting most species of babesia in different animals e.g horse (B. Caballi), cattle (B. bovis&B.Bigemina) , sheep & goat (B.motasi&B.ovis) , pig (B.suis) and dog (B.canis).
dose: horse 0.3 0.5 mg/kg B wt., Cattle , sheep & pig 0.5 mg/kg B.wt.

It must be give s/c at conc. 5 % in all animals except sheep and dog 0.5 %.

Side effects: It possesanticholineestrase activity overcomed by pre-administration of atropine. It stimulate release of histamine overcomed by pre-administration cellular oxidation .
Toxicity: Sever shock may occur with rapid fall in blood pressure resulting in sudden death. In other cases muscle tremors, salivation, urination and defecation these symptoms may persist for 6-10 hours.

3-amicarbalide isethionate

It is chemically related to quinuroniumsulphate and replaced it because of low toxicity .
Dose & route:can be used 5-10 mg/kg .B. wt I/M, S/C or by slow I/V .thehaemoglobin level in urine fall considerably within 48 hours but may need second dose after 24 hour from the first .

4-Imidocarb (Imizol)

It is recommended for prophylaxis and treatment of babesiasis and anaplasmosis .

Dose & route: Can be given by I/M and S/C

Babasiasis therapy Cattle 1.2 mg/kg B.wt., Horse 2.4 mg/kg B.wt., Dog 6 mg/kg B.wt

Anaplasmosistherapy Cattle 3 mg/kg B.wt

**needs withdrawal period 23 days before slaughter .

4-Diminazene aceturate (Berenil)

It is mainly a trypanocidal drug and also active as babesiocidal in cattle, sheep horse and dog given at dose of 3.5 mg/kg I/M or S/C.

IV-Drugs for anaphasmasis and thileriasis

These are drugs used for treatment of anaplasma or thileria infection in animals and they include:

1-Tetracylines

Can be useful to treat thileria&anaplasma but must be given early and in large dose for long period

2-Dithiosemicarbazone

Given I/V daily for 10 days completely eradicate anaphasmamarginalae. It is synergistic to tetracycline with less toxic effects.

3-Imidocarb

A babesiocide and of value in treatment of anaplasma and thileria.

4-paravaquone (clexon)

Given as single curative treatment for thieleria in cattle at a dose of 20 mg/kg B.wtI/M.

5-Buparva quone (Butalex)

As parvaquone but at a dose of 2.5mg/kg .B. wt

Tryopanocidal drugs

These are drugs used for treatment of trypanosome infection

1-Quinapyramine chloride and sulphate (Antrycid)

Sulphate salt is water soluble so it rapidly and short acting while chloride is slightly soluble, slowly absorbed and long acting used as prophylactic.

Action and uses: It is active against T. congolense, T. evansi, T. vivax, T. equiperdum, T. equinum and less active on T. brucei. The drug act by inhibition of growth and cell division.

Dosage: given s/c at concentration 10 %

Weight of animal	dose
Less than 150 kg	4.4 mg/kg B. wt.
150-200 kg	1 g
200-350 kg	1.5 g
over 350 kg	2 g

Side effects:

It is histamine releaser, anticholinestrase activity, and cause local reaction at the site of injection may cause sloughing. These side effects can be overcomed by pre-administration of antihistaminic and atropine.

2-Phenanthridinium compounds

They act by inhibiting trypanosomal cytoplasm division cross resistance frequently occur between them. Includes dimidium bromide, Homidium bromide, pyrithidium and metamidium.

a-Homidium bromide (ethidium)

It is active against T. congolense and T. vivax, some activity on T. brucei with some prophylactic action but inactive on T. evansi.

dosage: Administered by deep I/M to avoid sever local irritation from s/c injection. It serves both curative and prophylactic.

b-Pyrithidium (prothidium)

It is prophylactic against T. conglense, T. Vivax and T. brucei, giving protection for 6-8 months and two months in areas of great risk. it can be administered by s/c or deep I/M but local swelling at the site of injection can be expected. dose 2 mg/kg. B.wt.

3-Dimenazene aceturate (Berenil)

It is effective against T. Viva x and T. congolense less on T. brucei.

Dose: for bebasia, T. vivax and T. congolense 3.5 mg/kg b.wt and mg/kg b.wt for T. brucei by I/M or s/c injection.

4-Suramin (Naganol)

It has marked curative and less usefull prophylactic prosperities against T. evansi, T. brucei, T. equinum and T. equiperdum but inactive on T. vivax and T. simiae.

Dosage: Horse 7-10 mg/kg .B.wt. repeated weekly for 3 weeks. Camel 8-12 mg/kg .B.wt. Cattle 12 mg/kg B.wt.

Suramin is potential toxic for its very narrow therapeutic index, horses and donkeys are very susceptible but camels are resistant.

Toxicity:

Symptoms of liver, kidney spleen and adrenal gland damage.

N.Bsuramin seems to be synergistic potentiator of phenanthridium and quinapyramine derivatives.

Prophylactic complex:

These being slowly absorbed and valuable as prophylactic.e.gsuraminprothidium and suramine . Homidium give protection for 8 months.

Antiseptics and Disinfectants

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Terminology:

1-Sepsis: means presence of live pathogenic microorganisms (M.O.)

2-Sterile: means no living microorganisms.

3-Santize: means to reduce the number of microorganisms to a safe level.

4-To inhibit or kill M.O: means bacteriostatic and/or bactericidal, viricidal, fungicidal.

Ideal antiseptic or disinfectant must be:

1-highly effective at low concentration against all M.O. 2-effective in the presence of organic matter and not injures to tissues. 3-soluble in water, stable, not corrode metals and penetrates tissue cervices and incompatible with other drugs. 4-safe, no adverse effects, does not harm living tissues, fast acting, long duration, odorless, non staining, not absorbed into the system of animal in amounts that may have adverse effects.

Phenol coefficient

Phenol coefficient is the concentration of disinfectant which has the same antibacterial activity of phenol solution of 1 % concentration.

Important of phenol coefficient

1-Calibration of the effectiveness of disinfectant, this calibration must under the same conditions of temperature, duration of action, bacterial concentration and strain.

2-The higher the phenol coefficient, the more potent is the disinfectants.

General mechanisms of antimicrobial action of antiseptics and disinfectants

1-Coagulation of protein of bacterial cells. Deamination of cellular protein.

2-Change permeability of cell membranes, leading to loss of essential substances from the cell and or entry of unwanted substances into cell.

3-Interfere with enzyme systems:

a-by inactivating enzymes, through attaching to sulphhydryl groups.

b-by competitive and non-competitive inhibition of metabolic pathways by chemical analogues.

c-by oxidation and reduction reactions.

Factors influencing action of antiseptics and disinfectants

1-Potency, which is related to all of the following:

a-concentration of the drug, usually given as a % solution.

b-duration of time in contact with organisms.
c-bacteristatic-weak concentrations. Bactericidal-higher concentrations.
2-Temperature of the isolation which is the environment of the microorganisms. a-heat increases effectiveness. b-cold decreases effectiveness.
3-Nature of media: clean surface is ideal:
a-organic matter has a protective effect upon microorganism.
b-disinfectants have poor penetrating power.
c-hardness of the water used for making a solution dissolved minerals may inhibit the antimicrobial action of the drug.
d-the pH of media. There will be an optimum pH for the action of drug depending on the microorganism and the pH changes may affect bacteria, pH changes may affect the disinfectants.
4-Type of M.O. involved:
a-viruses or fungi or bacteria. b-vegetative or spore forms of bacteria
c-acid fast and non acid fast.
5-Numbers of M.O.
6-Drug antagonisms. Usually physical or chemical incompatibility between the drug and the environment and / or between or more drugs used concurrently.

Classification of disinfectant and antiseptic

I-Physical: 1-ultra violet light 2-dessication 3-dry heat, high temperature and flame. 4-moist heat, steam and steam under pressure. 5-washing, scrubbing 6-irradication

II-Chemical

1-oxidizing agents

a-halogens…..e.g….chlorine

nascent O2

b-peroxides: $H_2O_2 \xrightarrow{\text{----------}} \text{kill M.O.}$

c-pot. permanganates 1/5000 releasing nacent $O_2 \rightarrow$ has a germicidal power.

2-Reducing agents

e.g….Formaldhyde: An irritant gas, 40 % in water forms formalin which kill most M.O. (1: 80 in water).
Mode of action: acts by combining with amino group on bacterial cell surface.
Uses: 1-It forms toxoids with bacterial toxins. 2-It is used as urinary antiseptic in acid urine by its liberation from hexamine in acid medium. 3-For fumigation of buildings (formalin and pot. permanganate are mixed 5:3) liberating formaldehyde.

N.B. Formaldehyde not affected by organic matter.

3-Heavy metal disinfectants

e.g….Salts of silver and mercury.

Action and mode of action:

They are bacteriostatic acting by reacting with SH group of bacterial enzyme.

Uses: a-mercury salts:

i-mercuric chloride used as skin antiseptic.

ii-mercuric nitrate and oxide which used as oint. to the eye.

iii-bin iodide of mercury: 1 % in lanoline as blister or counter irritants (1: 8).

iv-organic mercury compounds act as disinfectants by liberating mercury ions as thiomersolates for wounds, skin and instruments.

b-Silver salts:

i-silver nitrate…liberate free silver but irritant

ii-silver with protein…astringent. Non ionizing, non irritant, non corrosive

c-Copper salts: copper sulphate 1 %, astringent, fungicidal and germicidal.

d-Zinc salts: antiseptics including zinc sulphate, zinc oxide and zinc chloride.

e-Arenic: They includes…..arsanilic acid and Na arsanilate. They are used orally as intestinal antiseptic for E.coli.

4-Disinfectant acids and alkalies

a-Nalidixic acid…given as urinary antiseptics.

b-Mandelic acid…given as " "

c-Caustic Na. and quick lime…it is used as building disinfectants but the are corrosive.

5-Alchols (Ethyl alchol 70 %)

It is used as skin disinfectant, it acts by dehydration and ppt. for protein of bacteria.

6-Phenol and its derivatives

a-Phenol:

Uses: 1-used for comparison with other disinfectants.

2-used 2 % as powerful antiseptic but 0.5 % is ineffective.

Mode of action: Phenol dissolves the bacterial cell wall lipoids and kills the bacteria by combining with their protein.

b-Crysol: 1-Crysol is methylated phenol, less water soluble, more powerful disinfectants. 2-It is used at concentration of 0.5-1 % as intestinal antiseptic.

c-Lysol: 1-It is a mixture of crysol in water with soap. 2-It is less toxic but more powerful as disinfectant for objects but unsuitable for living tissues.

d-Chlorcrysol (crysol+chlorine): It is used as preservatives for solutions to be injected ten times more powerful than crysol.

e-Chloroxylenol (dittol): 1-Not irritant and suitable for intact skin.
2-Its phenol coefficient is 3 and effective in dilution 1:50.

f-Tymol : Urinary antiseptic.

g-Picric acid (triphenol amine): used as a paint in burns for ppt. protein of plasma

7-Dyes

a-Rosaniline

Action and mode of action: It acts as disinfectant by interfering with the glutamic acid metabolism of the M.O.

i-Brilliant green: Uses……1-It is used in 0.05-1 % for killing G+ve bacteria.

2-external use at 0.5 % alcoholic sol.

ii-Crystal violet and methyl violet stains: used as antiseptic for killing G+ve bacterial except streptococcus in sol……1-2.5 alcholic or 0.5 % watery.

b-Acridine derivatives

Action and mode of action: Acridines act as antiseptic by inhibiting synthetic processes of the M.O. by intercelating with its DNA.

i-Acriflavin: 1-its phenol coefficient is several hundreds
2-not inhibited by the serum. 3-act slowly in low concentrations 0.1 % saline externally and 0.01 % internally.

ii-Proflavin hemisulphate: 1-it is active in the presence of pus. 2-it is used at concentration of 0.2 % solutions which is least irritant.

c-Fluoreceine: It is a diagnostic dye for many diseases.

d-Azo dyes (Prontozil): Metabolized to sulphanilamide which act as antiseptic.

e-Methlene blue: It acts as antiseptic by carrying O2 as oxidizing agent.

8-Halogen disinfectants

a-Chlorine: Chlorine has a phenol coefficient 200 used to sterilize water.

Mode of action: Its action is due to formation of hydrochlorous acid which cause sterilization of water. They includes:

i-chlorinated lime by releasing Cl.

ii-Eusol (chlorinated lime + boric acid) used for wounds

iii-Chloramine T: It act by libarating chlorine oxidizing the bacterial protein, then halogenating the amino group. It is used for irrigating wounds.

iv-dichloramine: similar to choramine T but it is used as ointment.

b-Iodine: An efficient disinfectant as chlorine but has a counter irritant effect, rapidly inactivated by tissues and other proteins.

****Iodine preparations:**

i-Tr. iodine: used at concentrations 2.5 % as disinfectant for skin and cat gut.

ii-Lugol's iodine: watery sol. of I. Used at conc. 0.2 % for internal application.

iii-Iodoform: used as skin antiseptic (1:4 in talk powder) as dusting powder.

iv-Undecolium chloride-iodine----used as skin antiseptic.

9-Disinfectant detergents

a-Chlorhexidine (Hibitane):

Action and mode of action : It is potent bactericide acting by releasing the intracellular materials from the bacteria.

Preparations for used: solution at conc. 0.02-0.05 % (for wounds and burns), 0.5 % (for skin and instruments disinfection), Pessary or suspension as uterine antiseptic.

b-Soaps (Hard and soft): used as bactericide to some M.O.

c-Cetrimide (cetavlon):

It is used to clean the skin removing normal fat. Used as solution (0.1-0.5 %).

d-Benzalkonium chloride (Zephiran):

It is used at concentration 0.01-0.1 % alcoholic sol.

10-Other organic antiseptics:

a-Nitrofurans:

Action and mode of action:

Antibacterial action by inhibiting enzymes as pyruvic oxidase and aldehyde dehydrogenase, depriving the bacteria of energy essential for its growth given locally or systemically.

i-Furazolidone: acts on salmonella, shigella and Eimeria species (causing coccidian).

ii-Nitrofurazone: bactericidal for G+ve and G-ve and Eimeria (causing coccidian). It is used as bacteriostatic at 1-200,000 dilution.

**Nitrofurans are used as urinary antiseptic affecting M.O. resistant to sulphonamides.

b-Propamidine isoethionate (Brolene)

Uses: 1-As antiseptic for open wounds and burns as jelly or cream.

2-As therapy for babesias.

Antiviral agents

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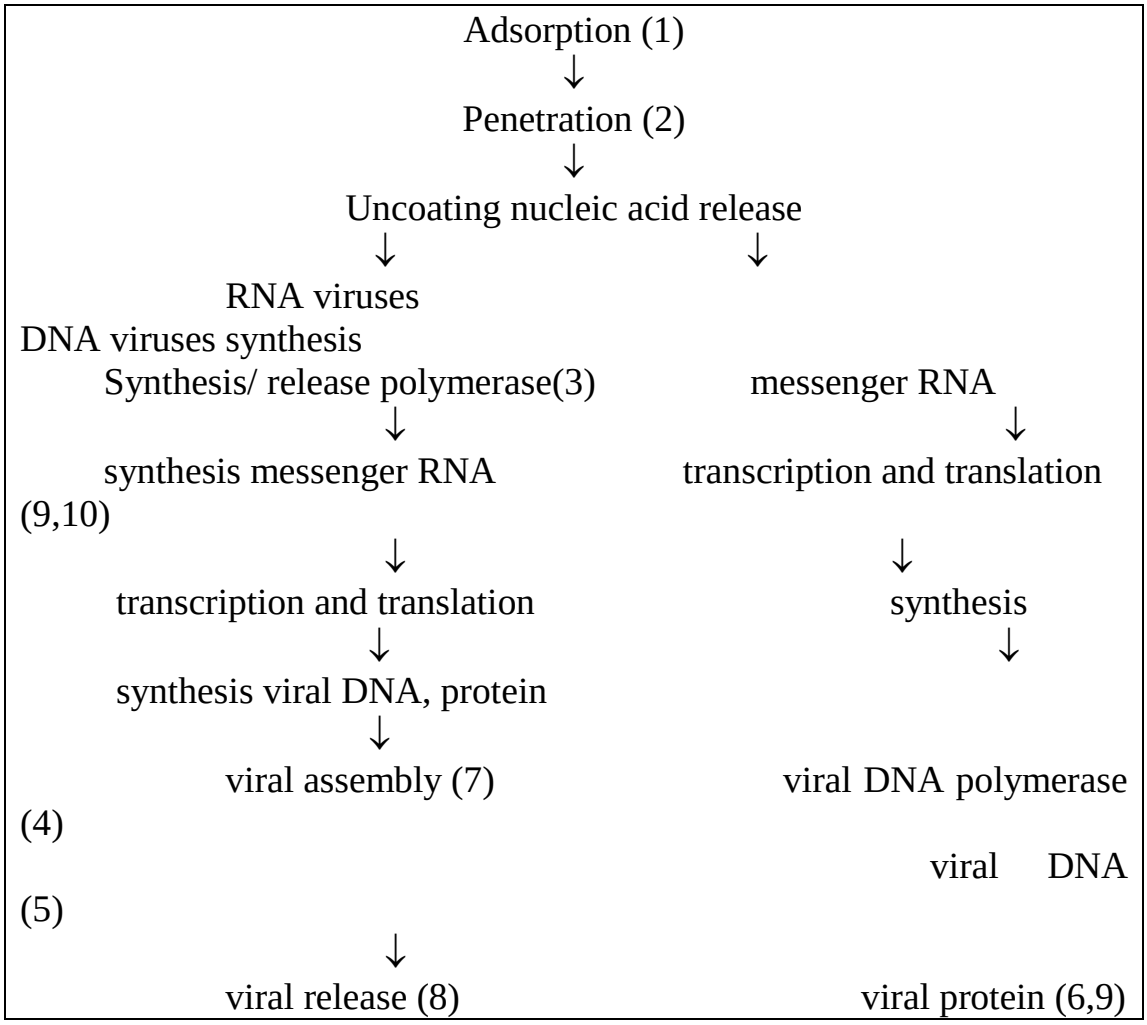
Clinical interest in the development of antivirals has until recently been weak primarily because many viral infections are acute and self-limiting but also because laboratory diagnosis of viral infection has been slow that results emerge too late to influence management. Moreover the parasite association of viruses and host cell led to belief that the drugs that interfere with the viral life cycle would inevitably be toxic to the host.

Action and mode of action:

Antiviral agents can act potentially at a number of points to viral replication by directly inactivating virus prior to cell attachment and entry ; by blocking attachment of virus to host cell membrane receptors and penetration, by blocking viral uncoating, by preventing integration of viral DNA into the host genome and by blocking transcription or translation into viral messenger RNA and proteins and by interfering with glycosylation steps.

Mechanism of action:

The mechanisms of action of some antiviral drugs as follows:
By inactivating the virus or blocking any step of viral cycle in the host cells.



Mechanism of action of some antiviral drugs:

1-heparin, poilanions 2-amantadine 3-benzimidazoles (vidarabine, acyclovir, phosphonoformate, bromovinyl, deoxyuridine ganciclorir, trifluridine).

4-doxuridine 5-ribavirin. 6-methizazone. 7-rifampin. 8-2-deoxy d-glucose. 9-interferon. 10-zidovudine.

N.B assembiy = fitting together of parts.

The most successful antiviral drugs are synthetic nucleosides that either inhibit viral DNA or RNA polymerase or act as chain termination after incorporation into nucleic acids. Many are too toxic for clinical use. Antiviral agents are generally only effective prophylactically or in the early stages of disease, while viral replication occurring. Rapid and early diagnosis is therefore important.

The obvious desirable characteristics of veterinary antiviral compounds are:

1-Broad spectrum efficacy. 2-Low cost.

3-Ease of administration. 4-Lack of drug residues (in some cases).

I-Inhibition of penetration of cells

1-Gamma globulin:

Passive immunization (intramuscular, intravenous and subcutenous)with immunoglobulins can prevent the entry of viruses into cells. The protective effect lasts several weeks but may not be complete (e.g. control canine distemper and rabies).

2-Amantadine:

Def:- Amantadine Hcl is a synthetic tricyclic amine with a symmetric structure. It is a water soluble stable powder. The antiviral activity of amantadine is limited to influenza A in animals and humans.

Pharmacokinetics of the drug:

The drug is well absorbed in the human after oral administration and is excreted unchanged in the urine. The half life is about 20 hours. Amantadine is most effective when used prophylactically but is moderately effective early in the course of clinical illness.

3-Rimantadine:

Is less toxic. In horses, use at 20 mg/kg shortened the duration of influenza virus shedding and was without toxic effect. Amantadine and rimantadine have been used successfully prophylactically in preventing influenza in experimentally infected chickens or turkeys by administration in water or food. Resistance has developed during clinical use.

II-Inhibition of intracellular protein synthesis

Inhibition of early protein synthesis:

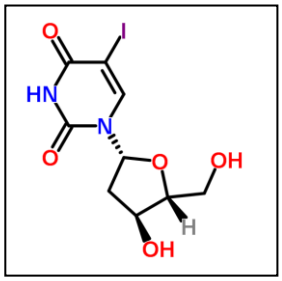
1-Bisbenzimidazoles:

Inhibition the formation of RNA polymerase in certain RNA virus infection, but resistance develops readily so that clinical results have been disappointing.

III-Inhibition of nucleic acid synthesis

1-Idoxuridine:

(structural formula of Idoxuridine)



It is active against herpes viruses. It is selectively inhibit viral replication in infected cells, where it converted to the iodoanalogue of thymidylate and incorporated into viral DNA, inhibiting virus specific DNA polymerase and also producing defective viral protein. Because of toxicity it is only applied locally. It is available as an ophthalmic ointment and solution.

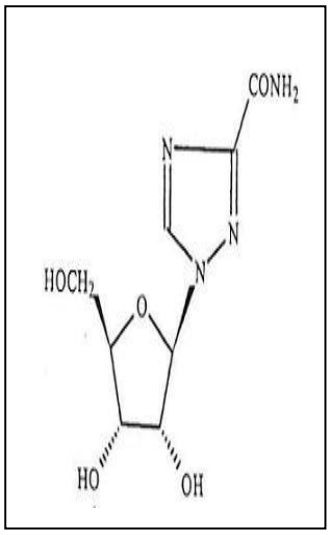
It has been recommended for the treatment of feline herpes virus keratoconjunctivitis and herpes keratitis in other species. (5 times, 0.1 % drops).

N.B. shedding = diffuse.

Disappointing = fail to fulfill the expectation or hope of.

2-Ribavirin:

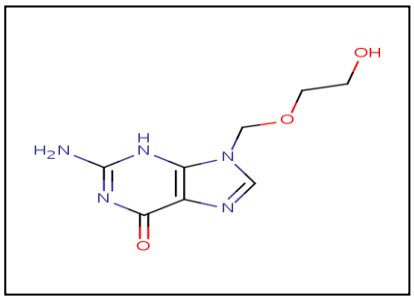
(Structural formula of ribavirin)



Is a synthetic nucleoside. It interferes with viral DNA synthesis by interfering with the formation of guanosine monophosphate, upon which DNA and RNA synthesis depend. It thus differs from other nucleosides described in its broad antiviral activity against many RNA and DNA viruses. It is also characterized by lack of viral resistance during clinical use and by low toxicity after systemic administration. In cats 75 mg/kg for 10 days in 3 divided doses produced profound thrombocytopenia and other sever effects. Work is needed to determine the potential use of ribavirin in veterinary medicine, although it may be limited by high cost of drug.

3-Acyclovir:

(Structural formula of acyclovir)



Clinical use: In an ointment is used successfully in local treatment of herpetic keratitis in human & animals. Activity against marks disease virus in vitro & vivo was described as low activity against feline herpes virus, which was enhanced by interferon. Further studies on a cyclovir's potential use in veterinary medicine are needed.

4-Trifluridine:

Trifluridine is an effective in the treatment of superficial herpes keratitis. Treatment is hourly for the first day , reduced to 5 times daily until corneal lesions are healed. Trifluridine is the drug of choice for herpetic keratitis because of its superior ability to penetrate the cornea.

IV-Inhibition of late protein synthesis

Methisazone:

Inhibits human pox virus (vaccinia, small pox) by inhibiting of protein required for the development of mature virus. It was ineffective in the treating experimental contagious pastular stomatitis in sheep. Methisazone might be used for local application in the early lesions of the bovine teat caused by cowpox or pseudocowpox viruses. The in vitro activity of methisazone against adenoviruses suggests possible applications in the prophylaxis of infectious canine hepatitis and equine and bovine respiratory diseases.

V-Inhibition of virus assembly release

2-deoxy-D-glucose

2-deoxy-D0glucose inhibits a wide range of enveloped DNA and RNA viruses. It interferes with the synthesis of the oligosaccharides that are part of the viral specific surface glycoproteins. The virus have decreased infectivity because of their inability to penetrate cells or to become uncoated. Clinical benefit has been claimed for topical application to initial lesions of genital herpes in women. Calves administered 20 mg/kg daily intravenous had no protection against experimentally induced respiratory infectious bovine rhinotracheitis (IBR) infection, but ocular instillation markedly reduced the severity of experimental Keratoconjunctivitis. A dose of 10 mg/kg daily intravenous apparently protected calves against the development of experimental respiratory syncytial virus infection, but the drug had no effect once clinical disease occurred. The drug has no potential application in the prophylaxis of canine distemper, equine influenza and parainfluenza infections.

Interferons

Def: Interferons are families of glycoproteins that exert non specific antiviral activity through cellular processes involving synthesis of RNA and protein

Characters:

1-Interferons possess antiviral. 2-Immuno-modulatory.
3-Antiproliferative effects. 4-It produced in most animal species.
5-They tend to be active in the species in which they are produced.

Types of interferons:

1-α (leukocyte) interferon 2-β (fibroblast) interferon…(both are released in response to viral infection). 3-Gamma interferon…(released from T-lymphocytes in response to antigen or mitogen stimulation)

N.B. The antiviral activity of interferon is indirect, by altering the host cell metabolism to impair synthesis and assembly of the viral components. Interferons express some of their activity as

lymphokines and immuno-modulators. The clinical role of interferons in prophylaxis and treatment of viral infection is of considerable interest in human and veterinary medicine, as in the antibacterial activity of interferon gamma.

Mechanism of action of interferon:

The antiviral effect of interferon results from induction of several proteins in exposed cells. Interferons are rapidly internalized after binding to cell membrane receptors. Interferons increase antibody production and natural killer cell activity as well as the expression of class IHLA antigen on the cell surface, thus enhancing recognition of virally infected cells by the immune system. Interferon gamma has distinct immuno-modulating effects, inducing class II HLA antigen expressing on macrophages. The drug has a central role in activating macrophages and thus has considerable potential clinical use in enhancing resistance to intracellular pathogens.

Antimicrobial activity of interferon:

-Interferons alpha and beta are active against a broad range of viruses.
-Interferon gamma has additional activity against intracellular pathogens.

Pharmacokinetics of interferon:

-Interferon alpha can be administered subcutaneous, intramuscular, intravenous or locally. Interferons are generally administered intramuscular and have serum half lives of 3-8 hours. Continued use of human interferon in animals is eventually accompanied by development of neutralizing antibodies.

Drug interaction of interferon:

-Synergism with other antiviral drugs has some times been described.
-Synergism of interferon gamma with azithromycin against experimental toxoplasmosis was described.

Toxicity and adverse effects of interferons:

-Fever and neutropenia was reported in calves treated with interferon alpha.
-Transient anorexia and weight loss has been described in cats.

Clinical applications of interferons:

1-They are used in the treatment of chronic viral hepatitis in cattle
2-They are used in the treatment intra lesional of some papilloma virus infections.
3-They are used in the treatment of herpes simplex infections.
4-They are used in the treatment of neoplasms, rabies and hemorrhagic fevers.
5-In cattle, intramuscular or intranasal treatments of calves with human interferon alpha reduced morbidity caused by bovine herpesvirus I and Pasteurella haemolytica, possibly due to the immuno-modulatory activity

of the drug. No antiviral effect was observed in calves infected with respiratory syncytial virus.
6-Calves treated with bovine interferon alpha were protected against experimental vaccine infection.
7-Recombinant bovine interferon gamma administered by the intramammary route considerably reduced the severity of experimentally induced E. coli mastitis in cattle as well as enhancing mammary phagocytic infection
8-In cats, oral dosage with bovine beta or human alpha interferon resulted in favorable solution of non-regenerative anemia after feline leukemia virus infection.
9-Treatment with high doses of human interferon alpha temporarily suppressed disease signs and increased survival time in experimentally induced feline infectious peritonitis.

Inhibition of assembly of viral particles

Rifampin

Rifampin inhibits DNA-dependent RNA polymerase in bacteria and mammalian cells. It also inhibits pox viruses but by a different mechanism. Rifampin prevents the assembly of enveloped mature particles. The block apparently occurs during the stage of envelope formation and is reversible upon removal of the drug.

Interferon inducers

In general, the use of synthetic interferon stimulators has not yielded satisfactory clinical effects in humans or in animals, probably because the quantities produced have been low. Virus-induced production of interferon in animals, using controlled non pathogenic viral infection, has given better results. Polyriboinosimic acid/polyribocytidylic acid and a synthetic polyribon-ucleotide, has been used to induce interferon in both humans and animals, but results in animals have been disappointing.

Immunoenhancers

e.g. 1-Cytokines. 2-Inosiplex. 3-Bacterial adjuvants.

Both bacillus colmette-Guerin and Corynebacterium parvum are non-specific adjuvants that increase the activation of macrophages through an effect on T-lymphocytes.

Drugs used in cancer chemotherapy

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Chemotherapeutic drugs are classified into:

I-Alkaylating agents

1-Cyclophosphamide:

Mode of action: Cyclophosphamide metabolized in liver to the active cytotoxic metabolites phosphoramide mustered and arecholine phosphoramide mustered is responsible for most of the antineoplastic effect of the drug. Resistance to treatment with drug develops in tumor cells to produce glutathione and obtain protection from oxidative damage. The excretion by the kidneys so the dose and dose interval must be considered in patients with renal disease.

Sid effects: Bone marrow suppression. Nausea and vomiting. Neutropenia and mylosuppression. The treatment cycle must not exceed one week due to severe neutropenia and thrombocytopenia. Hemorrhagic cystitis may occur. Alopecia occurs in dogs and cardiotoxicity occurs when cyclophoshamide used in combination with doxorubicin or dactinomycin.

Dosing regimen: Orally 50-100 mg/m^2 daily for 4-7 days/week according to the particular tumor protocol. Intravenous 200 mg/m^2 once weekly, but this protocol is dangerous mylosuppressive for some dogs.

2-Melphalon (phenylalanine mustered):

In dogs and cats, melphalon is used for the treatment of plasma call tumors, either plasma cell myloma or extramedullary plasmacytoma.

Side effects: Mylosuprression.

Dosing regimen: Orally, it should be given several hours before the animal feed. It is given in a dose 0.1 mg/kg for 7-10 days and then 0.05 mg/kg per day until remission is achieved. The drug is then given as a maintenance agent for 7 days out of every month at 0.1 mg/kg per day.

3-Chlorombucil:

Chlorombucil is derivative of nitrogen mustard. It is the slowest acting and least toxic of the alkylating agents used in veterinary medicine. The drug absorption occurred by passive diffusion when given orally before feed as food may interfere with its absorption.

Side effects: Marrow suppression. Myelosuppression induced when given daily for at least one month.

Dosing regimen: The dose for chlorombucil (0.1-0.2 mg/kg orally daily) for 4-7 days and then 0.1 mg/kg daily till remission occurs. Then maintenance protocol is indicated by the tumor that there is 0.1 mg/kg daily for 7 consecutive days a week flowed by 21 days.

Therapeutic use: Chlorombucil is used as chief support for treatment of chronic lymphocytic leukemia, small cell lymphoma, Waldenstrom's macroglobuline-mia and thymoma in dogs and cats. Activity may seen against plasma cell myeloma and ovarian carcinoma.

4-Nitrosoureas (Lomustine and Carmustine):

Pharmacokinetics: The drugs are very soluble and cross the blood brain barrier easily. Excretion occurs via kidneys so the patient with renal diseases must be considered.
Side effects: Both of nitroueas emetogenic immediately after administration. Prolonged bone marrow suppression is common with both drugs. In some cases, neutropenia may be noted severely.
Dosing regimen: Carmustine intravenous infusion (add to saline or 5 % dextrose in a dose of 50 mg/m^2 once every 6 weeks. Lomustine given orally in single dose of 60-75 mg/m2 once every 4-6 weeks.
Therapeutic use: In human to treat certain lymphoma. In veterinary medicine the drug used for treatment of CNS neoplasia. Lomustine also used in the treatment of canine mast cell tumors.

5-Dacarbazine:

Mode of action: It act against tumor cells by alkylation of nucleic acids.
Side effects: Local pain during administration. Concentrated solution of the drug are very irritant to veins and extravasation will produce sever phlebitis. Vomiting and nausea are common during the first few days of treatment.
Dosing regimen: Intravenous slowly gives the drug at a dose of 150-250 mg/m^2 daily for 5 days. Treatment is repeated every 3 weeks.

II-Mitotic inhibitors (vinca Alkaloids)

Mode of action: Vinca Alkaloids (plant extracts) are vincristine and vinblastine. Both drugs appear to act as spindle poisons by binding to microtubular proteins within cells, so they are used as anticancer agents.
Side effects: Neutropenia in cats. Anorexia and nausea in dogs and cats treat with vincristine. Myelosuppression. Local phlebitis and sever pain when vinca is extravasated. Sever nerve fiber degeneration and focal axonal swelling with demylination of peripheral nerves.
Dosing regimen: Vincristine given intravenous in a dose 0.5-0.75 mg/m^2 once weekly according to the treatment protocol used. Vinblastine given intravenous, begin at 2 mg/m^2 once every 2 weeks. At each cycle, increase the dose 0.25 mg/m^2 until myelosuppression is seen. Then give the maintenance dose (one treatment smaller than the dose that produce leucopenia).

III-Antitumor antibiotics

1-Doxorubicin:

Mode of action: Doxorubicin is directly cytotoxic, binding irreversibly with DNA and preventing both DNA and RNA synthesis. Cellular damage caused by doxorubicin results in enzyme catalyzed, iron mediated free radical formation, which produces further tissue damage.
Pharmacolinetics: After intravenous administration, doxorubicin is metabolized in the liver to active and inactive metabolites. The drug is excreted primarily in the bile but persists in the plasma for prolonged periods
Side effects: Cardiotoxicity in dogs and cats from free-radical damage to the myocardium, with oxidation and death of myocardial cells in the presence of iron. Renal damage in cats with chronic treatment with doxorubicin. Anorexia

in dogs and cats. Myelosuppression occurs in dogs and cats. Alopecia occurs in dogs. Phlebitis if doxorubicin is extravasated.
Dosing regimen: In dogs is 30 mg/m^2 every 3 weeks for adult dog. At least 5 minutes should be taken for intravenous infusion.
Therapeutic use: In dog and cat lymphoma, leukemias and certain sarcomas and carcinomas. Doxorubicin has synergestic action with cyclophosphamide in the treatmen of some sarcomas.

Other antitumor antibiotics:

A-Dactinomycin (Actinomycin D). B-Bleomycin. C-Mitoxantrone.

IV-Antimetabolites

1-Methotrexate:

Mode of action: Methotrexate exerts its cytotoxic effect by competing for a binding site on the enzyme dihydrofolate reducase. This reversible binding prevents the synthesis of folate, which is important in the production of the purine nucleotides and thymidine.
Pharmacokinetics: It is given intravenous infusion. Excreted unchanged (80-90 %) in the urine of the human within 24 hours.
Side effects: GI disturbances. Hepatic dysfunction. Myelosuppression.
Dosing regimen: The oral dose is 2.5 mg/m2 given daily for 5 days followed by a 2 days rest period. This is repeated weekly until remission is achieved. 10 mg/m^2 given twice weekly followed by a 7-day rest period would be another acceptable protocol.

2-Another antimetabolities:

e.g. (5-Fluorouracil, Hydroxyurea)

V-Platinum drugs

Cisplatin:

Mode of action: Cisplatin acts as antitumor drug by its cytotoxic effects are considered to be due to alkalation of DNA.
Side effects: In cats, contraindicated for treatment with cisplatin in case of pulmonary oedema, because lead to dyspena and death within 48-96 hours after cisplatin administration. In dogs, nephrotoxic effect and acute GI toxicosis with nausea, anorexia and vomiting. If repeated doses, hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia & hypophosphatemia may occur due to renal tubular damage. Myelosuppression is generally mild but lengthy.
Dosing regimen: The dose in dogs 60-70 mg/m^2 given once every 21 days. Antiemetic given before treatment. Treatment are repeated once every 4 weeks as needed to maintain remission. Do not give cisplatin to cats.
Therapeutic use: 1-Used in dog carcinomas. 2-Cimplete remission occur in dog with metastatic seminoma. 3-Ovarian carcinoma treated with cisplatin.

VI-Miscellaneous drugs

1-L-Asparaginase:

It is an enzyme that derived from E. coli and that exploits a qualitative biochemical defects found in tumor cells. In acute lymphoid leukemia and

lymphoma, most malignant cells are dependant on extracelluar source of asparagines for survival.

Side effects:

1-Allergic reactions.

2-Exrteme facial oedema, swelling and pain at the site of injection in dogs after 24 hours of L-asparaginase administration.

Dose regimen:

Dosage is 10,000 to 20,000 i.u/m2 weekly or as part of combination protocol. It is given subcutenous, intravenous or intramuscular.

N.B. Intravenous injection must be very slowly about 30 minutes (infusion of Nacl or 5 % dextrose)

Therapeutic use:

The drug is used in the treatment of lymphoma and lymphoid leukemia

2-Piroxicam:

Piroxican is a non steroidal antinflammatory used in animals. Oedema, erthema and tissue proliferation can be inhibited by administration of the drug.

3-Corticosteroids:

Several glucocorticoid hormones are used in the treatment of patient with cancer. e.g hydrocortisone, prednisone and dexamethasone.

Drugs affecting the endocrine system

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Definition

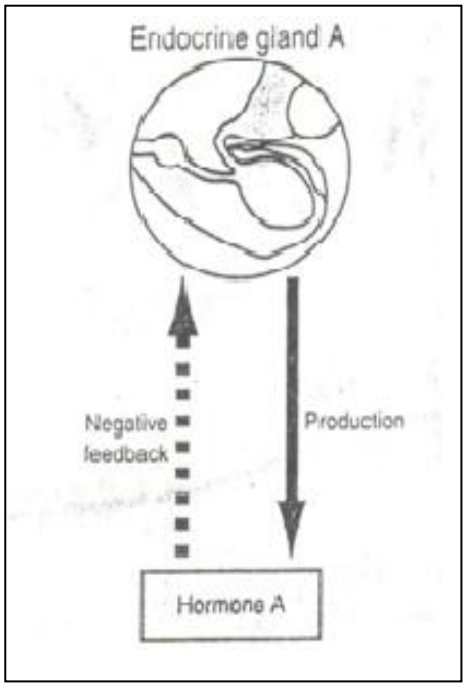
1-Endocrine gland : is a gland secreting active materials (hormones) in a very small amount directly into the blood stream.

2-Hormone : is a messenger control the functions of tissue and organs or is a specific chemical stimulus released in a very small amounts into the blood stream by an endocrine or ductless gland

*The endocrine system is composed of the thyroid gland, ovaries, testicles, pancreas, adrenal glands and other glands that produce hormones.

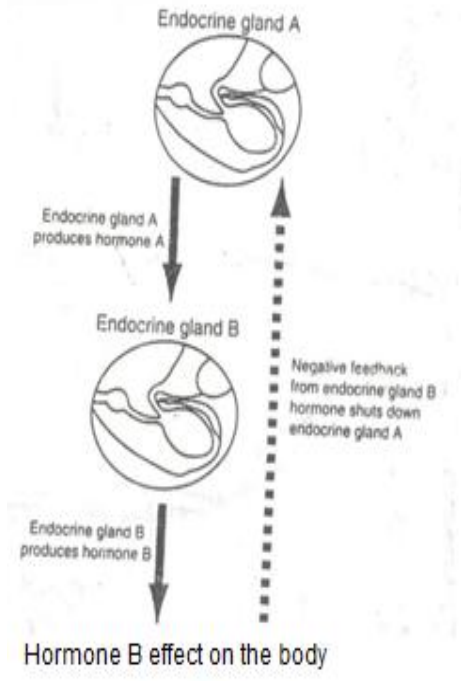
The negative feed-back mechanism

All endocrine systems are regulated by a feed-back mechanism in much the same way as the temperature inside a house and a thermostat regulate the activity of a furnace. In a house, the furnace produce heat until the thermostat detects that the interior environment is warm enough and sends a signal that turns off the furnace. This signal from the thermostat to the furnace to stop or inhibit its heat production is called negative feed-back mechanism.



As shown in Figure (1) endocrine gland A is responsive to circulate levels of a hormone that it produces. When concentrations of that hormone fall below a certain level, endocrine gland A begins to produce the hormone again in a way that similar to how the furnace produces heat when the temperature drops below a certain points. As concentrations of hormone increase to desired levels, the negative feed-back from the presence of the increased hormone causes endocrine gland A to shut itself off. When the body metabolizes the hormone and concentrations drop below the critical concentration again, the negative feed-back is removed from the endocrine gland A and it begins to secrete hormone again.

Endocrine regulation and negative feed back are more complex. As shown in Figure (2), endocrine gland A produces a hormone that stimulates endocrine gland B to produce its hormone. When sufficient gland B hormone is circulating in the body, the negative feed-back inhibition on endocrine gland A, decreases endocrine A's stimulating hormone. Endocrine B is no longerstimulated and stops producing hormone until endocrine gland B's hormone drops low enough and the cycle starts over again. If the drug injected initiated (mimic) endocrine gland A's hormone, the drug would stimulate endocrine B, resulting in increased production of endocrine gland B's hormone. Exogenous hormone or hormone like drugs can easily upset the balance and produce unintended effects.



Regulation of endocrine glands when more than one gland is involved.

Pituitary gland

Pituitary is the master gland, under control of releasing hypothalamic hormones. It secretes trophic or tropic hormones which control the functions of all endocrine glands.

I-Anterior pituitary hormones (Adenohypophysis)

Definition:

*The adenohypophysis is a polypeptide hormones that stimulate the activity of other endocrine glands secrete at least seven poly peptide hormones, four of which stimulate the secretory activity of other endocrine glands.

They includes:

A-(1-4) stimulate other endocrine glands

1-Follicle stimulating hormone (FSH) 2-Lutenizing hormone (LH) or interstitial stimulating hormone (ICSH) 3-Thyrotrophin hormone (TSH) 4-Corticotrophin (ACTH)

B-(5-7) the hormones produce their effects directly at their appropriate targets

5-The growth hormone (GH) 6-Prolactin ….. see reproductive system

7-Melanocyte stimulating hormone (MSH), also known as intermedin

1-Growth hormone (GH) (Somatotrophin)(STH)

Definition

*GH is a polypeptide has molecular weight around 22000. In man GH has 191 aminoacid residues and a single chain containing two disulphide cross links

Actions

*The main action stimulate growth

*Other actions of GH: 1-increase protein synthesis (anabolic action) 2-Promote amino acids uptake and favours a positive nitrogen balance (growth promoters in cattle acts as GH) 3-GH elevate glucose levels in the blood 4-GH increase plasma free fatty acids 5-GH stimulate synthesis of the growth factors by liver and kidneys called somatomedins A 6-It stimulate other somatomedins DNA synthesis

Mode of action of GH

Growth hormone acts in part indirectly in that it stimulates the synthesis of agents called somatomedins by the liver and kidneys. These growth hormone dependent factors are of unknown chemical structure. Somatomedin A, also known as sulphation factor, is involved in the sulphation of chondroition and is an important anabolic agent in cartilaginous growth. Other somatomedins stimulate DNA synthesis, glucose and amino acid transport into cells, and may be responsible for the continued effect of pulse released GH.

Therapeutic uses of GH

1-Treatment of pituitary dwarfism

2-As meat growth factor in animals but its side effect is diabetogenic

2-Prolactin *See reproductive system

3-Melanocyte stimulating hormone (MSH) or intermedin

Chemical structure

α MSH…is a 13 amino acid residue poly peptide chain

β MSH…contain 18 residues

Source

These hormones are found in the anterior and posterior pituitary extracts

Action

*Their function is stimulation of melanin synthesis in melanocytes. Both a releaser (MSH-RH) and a release inhibitor (MSH-RIH), a tripeptide in cattle) exist. The darkening of skin color in lower animals is achieved by MSH activity. Melatonin, a hormone released by the pineal gland, causes skin lightening by aggregation of melanophores i.e. by opposing the melanophore dispersing action of MSH. Melatonin has been used in attempt to treat acanthosis nigricans in the dog at a dose of 2 mg subcutaneously at 2-day intervals for 8 days then 2 mg for two weeks.

4-Thyrotrophic hormone (TSH)

Thyrotrophic hormone (TSH) is a glycoprotein with a molecular weight of about 30000. It stimulate the thyroid gland to secrete thyroid hormones.

Mode of action

It acts at the membrane of thyroid cells, probably via adenylate cyclase. It increases the metabolic activity of the cells, including the synthesis and release of thyroid hormones. Both hypertrophy and hyperplasia follow lengthy exposure of the gland to TSH.

Control of secretion

The adenohypophysis secretes TSH in response to a hypothalamic releasing hormone (T-RH). While this is influenced in a feed-back mechanism by thyroid hormones overall regulation, as with other trophic hormones is more complex and allows of other inputs such as temperature T-RH output is increased in response to low temperature via a neuronal input at the T-RH secretory cells. This response can be reproduced with noradrenaline or dopamine and inhibited by 5-HT. T-RH is a tripeptide, active by mouth or intravenously and also causes the release of prolactin. The physiological significance of this finding is obscure, because prolactin and TSH. Concentrations do not normally increase in phase because GH-RIH (Somatostatin) can inhibit the release of TSH by T-RH it is possible for T-RH to bring about the release of prolactin alone.

Therapeutic uses of TSH

1-As test for thyroid function 2-Treatment of hypothyroidism

5-Follicle stimulating hormone (FSH) and Luteinizing hormone (LH)

*See reproductive system

6-Corticotrophin (ACTH)

*It is 39 amino acid containing poly peptide hormone with interspecies variation.

Actions and mode of action

ACTH stimulate the middle and inner zones of the adrenal cortex to synthesize glucocorticoids. Primarily cortisol and corticosterone. Aldosterone production by the outer layer is little influenced by the pituitary. ACTH action causes a rise in intracellular cyclic AMP concentration, this is followed by a number of changes, including the increased synthesis of enzymes active in steroid biosynthesis and the provision of co-factors. In this way ACTH increases the mitochondrial conversion of free cholesterol to pregnenolone, the rate limiting first step in steroid biosynthesis. This reaction also requires ascorbic acid, Ca^{++},

oxygen and NADPH. The cholesterol is derived from storage esters, again under the influence of ACTH which is able to increase the gucocorticoid content of adrenal vein blood in minutes. This rapid response is compatible with the absence of a glucocorticoid storage mechanism and the dependence of steroid plasma concentrations on direct negative feed-back regulation. Adenohypophyseal ACTH output is stimulated by a hypophyseal corticotrophin releasing factor, C-RH, a 41 amino acid in sheep is itself is released in response to hypoglycemia and stress of all kinds. Thus the CNS enables the adrenal cortex to fulfill its function of increasing the ability of the body to withstand stress and also produces the circadian rhythm in plasma glucocorticoid concentrations.

Synthetic preparation

(Tetracosactrin) consists of 24 amino acid sequence, can be used without antigenic hazard. Natural ACTH is prepared by extraction of pituitary glands. Its half-life is about 15 minutes and so to obtain extended action depot preparations (in gelatin) are available for intramuscular injection.

Uses

1-ACTH used in Addison's disease in dogs

2-Measuring plasma cortisol level at 30, 60 and 90 minutes after ACTH administration

3-A primary pituitary deficiency is detectable by plasma ACTH assay alone by assay following the insulin induced hypoglycemia

Adrenal gland

The adrenal (supra-renal) glands secrete a group of hormones essential for life and can be classified into :

1-Cortical hormones :

*secreted from adrenal cortex and include 2 main groups :-

a-Mineralocorticoids

-Are responsible for regulating electrolyte balance

-e.g…aldosterone…its secretion is regulated by rennin angiotensin system

b-Glucocorticoids

-Principally act on carbohydrate metabolism

-e.g…cortisol…regulated by ACTH from anterior pituitary

-it is powerful glucogenic and anti-inflammatory

-hyperactivity of adrenal cortex produce cushing syndrome while hypofunction causesAddison's disease

2-Adrenal medulla is the site of synthesis, storage and release of adrenaline which is fully discussed in autonomic nervous system

Effect of corticosteroids :

*Mineralocorticoids act on the kidney to increase reabsorption of sodium, chloride and water and increase loss of potassium, phosphate and calcium
*Mechanism of action involves synthesis of protein in target cell may be the sodium carrier itself
*Overdose of glucocorticoids posses significant mineralocorticoid effect
*Physiological dose of glucocorticoids enhance water excretion by increasing glomerular filtration and decrease water reabsorption
*Glucocorticoids increase gluconeogenesis (i.e. production of glucose from non carbohydrate by deamination of amino acids and increase urinary nitrogen output)
*Glucocorticoids induced hyperglycemia accompanied by decrease uptake of glucose and resistance to insulin
*Glucocorticoids favor lipolysis and thus provide glycerol for gluconeogenesis
*Long term administration of glucocorticoids causes muscle wasting and redistribution of fat
*Immunity of the body is decreased by glucocorticoids. Lympholytic response is a reduction in size and activity of lymphoid tissues and a diminution of count
*Decrease antibody production and eosinophil count
*Depress acute inflammatory response, prostaglandins synthesis, cellular infiltration, exudation, fibrosis and wound healing

Mode of action

1-Steroid hormones are bound partly to albumin mainly to a transport protein (in the case of cortisol, a globulin called transcortin). This complex release the steroid at appropriate cells where the steroid enters. Inside the cell the steroid reacts with a specific receptor protein in the cytoplasm. This complex after a conformational changes enters the nucleus. Within the nucleus the complex interacts with an acceptor and becomes attached to a chromatin protein. In this position the synthesis of proteins is influenced by an action which increases the transcription of mRNA leading in the liver to the synthesis of enzymes involved in the gluconeogenesis and glycogenesis. In the adrenal medulla, the synthesis of the enzyme convert adrenaline into adrenaline is stimulated by corticosteroids. In other tissues such as skin, the glucocorticoids causes a reduction in DNA synthesis and cell division.
2-Other mechanisms of action for steroids have also been proposed including the involvement of cyclic amp production. The inhibition of prostaglandin synthesis is believed to take place at the level of phospholipase, the enzyme which fees arachidonate from membranes as the first step prostaglandin biosynthesis

Synthetic steroids

1-Hydrocortisone 2-Prednisone 3-Prednisolone 4-Methyl prednisolone 5-Flumethasone 6-Dexamethasone

Therapeutic uses of glucocorticoids

1-Treatment of bovine ketosis in dairy cattle and pregnancy toxemia in sheep

2-Stress, trauma and shock 3-Inflammation of eye, skin and joints

4-Hypersensitivity reactions 5-Lymphoma as they have lympholytic action

6-Induction of parturition

Contraindication

1-Late pregnancy especially for C_{16} methylated corticosteroids except in pregnancy toxemia

2-Deep corneal ulcer or other wounds after surgical operation as it retard healing

3-Cardiac insufficiency as they have depressive effect on circulatory system

Dosage

1-Prednisolone

-large animals….100-200 mg i.m daily

-small animals….2-20 mg i.m initially followed by oral therapy (dogs 0.5-1 mg/kg b.wt. daily by moth while in cats 1 mg/kg b.wt. daily by mouth)

2-Dexamethasone

Parentral…-Horse, cattle: 10-30 mg., Foal, calf, sheep, goat and pigs: 2-5 mg.,

Dog: 0.5-2 mg., Cat: 0.25 -0.5 mg

Intra-articular…-Large animals: 2-10 mg

Peri-articular….-Small animals: 0.25-5 mg

Oral….-Small animals: 0.25-5 mg

These daily dosages should be divided. Initial doses may be maximum or near maximum but once symptoms are controlled doses should be reduced to maintenance levels quoted doses are guideline figures only and should in each case by adjusted according to the circumstances

Steroid inhibitors

a-Hyperaldosteronism as a primary or secondary feature occurs in man. It can be treated with a spironolactone a competitive antagonist of aldosterone

b-Dichlorodiphynyl dichloroethane (DDD) is a drug which can cause destruction of the adrenal cortex in dogs or suppression of glucocorticoid production at lower dosage. It is also known as mitotane, as it is closely related to DDT.

c-Amphenone B is a rather toxic drug which is able to block the β hydroxylation of pregnenolone and so inhibits steroid biosynthesis.

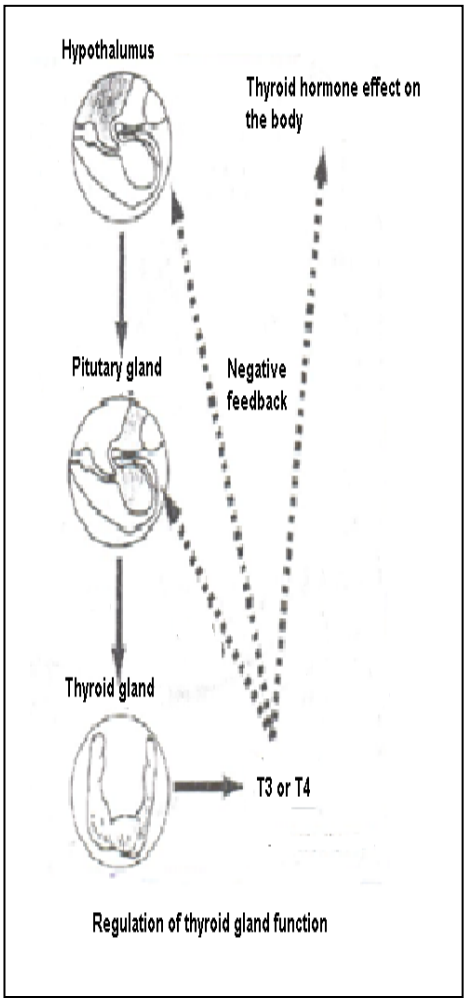
Metyrapone prevents the 11 β-hydroxylation of the immediate precursor of cortisol. It is used to suppress glucocorticoid output so as to induce the pituitary to release ACTH, in a test to distinguish between primary and secondary adrenal hypofunction

Thyroid gland

It is an endocrine gland consists of two lobes lies on both sides of larynex joined by isthmus anteriorly. The extract of thyroid gland contains thyroid hormones, thyroxine (T_4) and tri-iodothyronine (T_3) which is more potent than thyroxine.

Thyroid hormones synthesis

The thyroid follicle cells contain vesicles of non iodinated thyroglobulin which rupture release thyroglobulin (TG) into follicular lumen, the iodide diffuses down concentration gradient and oxidized by thyroid peroxidase
enzyme to iodine then combines with tyrosine of thyroglobulins forming mono and di-iodotyrosine units and tri-iodothyronine is formed by combination of one monoiodo tyrosine and one di-iodotyrosine.



Regulation of thyroid gland function

Secretion of thyroid hormones

(TSH) a glycoprotein hormone produced by anterior pituitary stimulate synthesis and secretion of thyroid hormones in a feed-back manner to the hypothalamus and pituitary (Figure).

Metabolism of thyroid hormones

1-Liver conjugates T_4 to glucuronides and sulphate which are excreted in bile
2-De-iodination of thyroid hormones using de-iodinase enzyme (require selenium for activity0 which is present in liver, kidney, muscle, thyroid, CNS, placenta and skin.

The iodine is recycled in thyroid hormones synthesis where the de-iodinated metabolic products are of no thyromimetic activity.

Physiological and pharmacological action of thyroid hormones

1-Thyroid hormones are anabolic in physiological level working in conjunction with growth hormone, insulin and protein synthesis but it is catabolic in hyperthyroidism.

2-Increase heat production and oxygen consumption by stimulating Na,K-ATPase in all tissues except brain, spleen and testis (i.e. increase BMR).

3-Essential for growth and maturation hence hypothyroidism cause dwarfism and impaired mental development

4-Increase glucogenolysis and gluconeogenesis i.e. insulin antagonistic activity, also increase synthesis and degradation of cholesterol and stimulate lipolysis with releasing of free fatty acids and glycerol

5-Necessary for normal hair skin turn over

6-On myocardium, causing direct positive inotropic effect, myocardial hypertrophy and increase responsiveness to adrenergic stimulation

7-Stimulate the synthesis of many protein associated with normal nerve and activity, thus hypothyroidism cause myopathies

8-Hypothyroidism decrease GIT motility

9-Essential for normal reproductive cycling. Hypothyroidism cause reproductive disturbances, infertility, lack of libido, testicular atrophy and hypospermia

10-Hypothyroidism reduce phagocytosis of W.B.Cs

11-Increase erythropiosis and 2,3 diphosphoglycerate content of RBCs (increase O_2 dissociation from Hb at the tissue)

12-Thyroid hormones influence normal secretion and metabolism of hormones. Hypothyroidism cause glactorrhea due to increased prolactin secretion

Synthetic thyroid hormones

Thyroxine sodium (T_4)

It is synthetic posses the same activity of thyroid extracts but 0.1 mg is approximately equal in activity to 60 mg of the dried extract. After oral administration of thyroxine, half the dose is absorbed and cause increase in metabolic rate, increase carbohydrate metabolism causing depletion of liver glycogen. Also ↑ catabolism of fat and protein. It increase urinary salt, nitrogen and water. Increase sensitivity of cardiovascular system to catecholamine

Liothyronine sodium (T_3)

It has more rapid onset of action, shorter duration and more potent

Toxicity

*Overdose will cause symptoms of thyrotoxicosis include :

-increased pulse rate, cardiac irregularities, restlessness and sleepless, osteoperosis, loss of weight and higher body temperature

Therapeutic uses

1-hypothyroidism or thyroid deficiency including hairless calves, hairless piglet, big neck, goiter and myxoedema
2-poor color of coat, obesity and edema
3-nymphomania in female cattle, loss of libido and depressed spermatogenesis in ram, boar and bull
4-bilateral alopecia in dogs

Dosage

1-Acute foetal iodine or thyroid deficiencies is given sodium or potassium iodide 1 mg/kg b.wt. orally. Thyroid hormones 1-2 mg/kg b.wt. in all species
2-Adult hypothyroidism rarely to occur. given thyroxine 1-2 mg/kg b.wt.

Iodine deficiency

Deficiencies of thyroid hormones and iodine are inter-related and have been shown to occur widely, causing considerable economic losses in herbivorous species, carnivorous species and birds. Clinical manifestations take the form of goiter and are most apparent in young animals. Animals may be born dead after prolonged gestation or completely without hair or edematous and with enlarged thyroid glands. Canine thyroid tumors and immune diseases that attack the thyroid gland usually result in primary hypothyroidism because the thyroid tumor cells are destroyed. The thyroid can not produce T_4 and T_3 regardless of how much it is stimulated by TSH. Goiter result in hypothyroid condition caused by lack of iodine in the diet. Hairless calves and piglets are perhaps the most common examples of hypothyroidism but sheep, goats, horses, dogs, cats and birds may all be similarly affected.

Adults may be affected but the condition is then less spectacular and takes the form of unthrift ness, loss of coat color and character and sometimes sterility (in male and female), with loss of sex drive in the male. Goiter may be due directly to iodine deficiency or may be associated with the goiterogenic effect of substances in the diet thiocyanates, possibly from linseed or clover, substances in Kale and possible goiterogens in other foods.

Mineral supplements usually contain about 0.03 % of potassium iodide or the more stable iodate (especially suitable or tropical climates)

*Daily doses of such a supplement should be :

-milk cattle (45-140 g), other adult cattle (60-180 g), calves (30-45 g), brood mares (60-120 g), other horses (60-90 g), ewes (15-22.5 g), lambs (5-10 g), sows (60-120 g), store and other pigs (30-60 g), laying hens

(220-400 g per 100 birds), chicks (30-60 g per 100 birds) and older chickens (90-160 g per 100 birds).
*Salt licks should contain about 0.05 % potassium iodide

Antithyroid drugs

*Drugs used to treat hyperthyroidism

Definition

-Hyperthyroidism is an increase in circulating concentrations of thyroid hormones. It is common in cats and it is associated with a hormone secreting thyroid tumor

-Hyperthyroidism in cats is best treated by thyroidectomy or by injection of radioactive iodine which destroy the tumorous thyroid tissues

-Radioactive iodine kills the tumor cells as appeared to methimazole which only controls hormone production without destroying tumor itself

1-Goiterogenes of plant origin

These are chemical compounds in some plants that inhibit the thyroid peroxidase enzyme (TPO)….e.g.

a-Plants of genus Brassica e.g rutabaga, cabbage and turnip

b-Broccoli and rape seed plants contain glucosinolates which are metabolized to thiocyanate, inhibitors of thyroid iodide uptake and organification

c-Cassava, lima beans and sweet potatoen contain cyanogenic glucoside metabolized to thiocyanate

2-Thioureylenes and thionamides

The thyroid organification and coupling steps are sensitive to inhibition by antithyroids thioureylenes and thionamides which block thyroid hormone secretion also they are actively concentrated in thyroid gland where they inhibit synthesis of thyroid hormone in the following steps:

i-block incorporation of the iodine into the tyrosyl groups of thyroglobulin

ii-block the coupling ofiodotyrosyl group to for T_3 or T_4 direct interaction of with thyroglobulin molecule 1 and 2 mediated through inhibition of (TPO).

Thioureylenes drugs commonly used in veterinary medicine are propylthiouracil and methamizole after initiation of the treatment there is delays in formation of serum thyroid hormones level until depletion of glandular store. Also block conversion of T_4 to more active T_3.

Side effects of propylthiouracil

1-Anorexia 2-Vomiting 3-Lethergy 4-Development of positive antinuclear antibody titer 5-Development of autoimmune hemolytic anemia 6-Development of immune mediated thrombocytopenia

Methimazole (Tabazole)

Is now the antithyroid drug of choice that has been used to control hyperthyroidism in cats by blocking the thyroid tumor's ability to produce T_3 and T_4. These drugs block the incorporation of the iodine into the thyroid hormone molecule. But the drug can not destroy T_3 and T_4 molecules.

*It is given at dose of 5 gm TID…will return the serum T_4 concentration to normal within 2-3 weeks

*Serum half-life of 4-6 weeks

*Bioavailability 45-98 % and intra-thyroid residence time 20 hours

Side effects

-occur in 20 % of cats, vomiting, anorexia, lethargy, bleeding, hepatopathy, thrombocytopenia, agranulocytosis, leucopenia, positive antinuclear antibodies

Carbimazole

It is carbthoxy derivative of methimazole, rapidly and completely metabolized to the parent drug responsible for antithyroid activity. It is used in the treatment of feline hyperthyroidism. Nonthioureylene antithyroid agent

I podate

It is a radiographic contrast used in treatment of feline hyperthyroidism at a dose of 15 mg/kg b.wt. twice daily

Radioactive iodine (^{131}I)

It is the most effective and appropriate treatment in bilateral toxic goiter in cats. It has 8 days half-life

Calcitonin

This hormone originates mainly in parafollicular C-cells of the thyroid gland. Procine calcitonin is a single-chain polypeptide of 32 residues which contains one disulphide bridge. It is pre-formed and released in response to hypercalcemia and exerts a hypocalcemic and hypophosphatemic effect. This is achieved by depressing the resorption of bone, perhaps by opposing the action of PTH which increases cyclic AMP concentration. The function of calcitonin seems to be the rapid control of hypercalcemia. It is accompanied by hyperphosphaturia. Calcitonin is available for use in man, where it finds application in suppressing the bone resorption of disease and in the treatment of hyperparathyroidism and vitamin D poisoning.

Parathyroid gland - Parathyroid hormone (PTH)

Parathyroid hormone is water soluble parathyroid gland hormone for subcutaneous or intramuscular administration. It contains not less than 100 parathyroid units per ml., the unit being defined as 1/100 of the amount necessary to raise the calcium content of 100 ml of the blood

serum of normal dogs by 1 mg within 6-18 hours after administration. A synthetic parathormone (PTH) analogue is now also available.

Action and uses

The parathyroids participate in calcium hemostasis by modulating the synthesis and release of PTH in response to plasma Ca^{++} concentration. They respond to low plasma Ca^{++} by secreting parathormone (PTH) which soon promotes active inorganic phosphate and calcium absorption from the intestine, followed by their mobilization from bone. PTH stimulates osteoclastic bone resorption and so elevates blood calcium levels, while calcitonin inhibits bone resorption and so corrects hypercalcemia. In the kidney, PTH acts rapidly via adenylcyclase activations to decrease phosphate resorption in the proximal tubule, increase calcium resorption in the distal tubule and increase the renal conversion of vitamin D to its active form (1,25-dihydroxy cholecalciferol).In acute hypocalcemic tetany, calcium solutions are requird because the delay before the onset of the effect of PTH unacceptable.

Lack of sufficient parathyroid activity causes the reverse of the above effects and as the level of blood calcium falls, muscle and general nervous irritability increases until the convulsive threshold is reached.

In hyperparathyroid states, the hormone causes a considerable increase in calcium and phosphate excretion, low serum phosphate and continuous calcium mobilization. In chronic cases, decalcification of the bones calcium levels are approximately doubled and the blood phosphate concentration also rises. Soft tissue metastatic calcification occurs, with eventual death from renal failure. Treatment is surgical.

Parathyroid extracts are unsuitable for oral administration, as digestive enzymes destroy the majority of any dose. It is recommended to given via subcutaneous or intravenous injections of 2-15 USP units for a dog. Owing to its effects on phosphate and its side effects, use of PTH in therapy should be confined to hypoparathyroidism. Even then, vitamin D, which appears to mediate the action of PTH, offers an acceptable alternative when combined with a high calcium diet.

In the treatment of experimentally induced hypoparathyroidism, it has been found that antibodies against parathyroid extracts develop and so the effect of a standard dose progressively reduced.

The endocrine pancreas (Islets of langerhans)

The pancreas plays a role in both endocrine (hormone) and exocrine (digestive enzyme) functions of the body

*There are three types of cells:

1-β cells secrete polypeptide hormone (insulin) blood glucose elevating hormone

2-α_1 cells release somtostatin which inhibit the release of growth hormone from hypothalamus

3-α_2 cells secrete single chain polypeptide hormone (Glucagon) opposes the action of insulin

Insulin

It is specific antidiabetogenic secreted from β cell of islets of langerhans. The major effect of insulin is to move glucose from the blood into tissue cells. Insulin also causes the liver to store glucose as glycogen and facilitates deposition of fat in adipose tissue. The net effect of insulin is to decrease blood glucose concentrations by enhancing distribution of glucose to body tissues. Lack of insulin results in diabetes mellitus, a disease characterized by high blood glucose levels or hyperglycemia and passage of glucose in the urine or glucosuria.

Insulin is standardized by bioassay to contain 20, 40 or 80 active units/ml. It is rapidly absorbed from site of injection produce maximum effect within three hours. More rapid effect achieved by I/V or I/M than by S/C. It is inactivated by gastrointestinal enzymes when given orally.

Types of insulin

A-Classified by their duration of activity as shown in table (1) into

1-plain insulin….short duration, effective for 8 hours and should be given twice daily

2-insulin zinc protamine or globin zinc insulin (40 or 80 unit/ml)

-intermediate duration, effective for 48 and 24 hours, respectively

3-insulin lent with high amount of zinc, reduce the solubility of insulin

-delay the onset and duration of action between plain insulin and protein insulin complex reach 18-24 hour given once daily by s/c injection. long acting

B-Classified according to species from which insulin is derived

-beef, pork or genetically engineered human type insulin

-N.B…Table (1) show comparison of types of insulin for dog and cat.

Table (1): Comparison of types of insulin used for dog and cats

Insulin type	Route of administration	Onset of effect	Duration of effect (dog)	Duration of effect (cat)
Regular	IV	Immediate	1-4 hr	1-4 hr
Crystalline	IM	10-30 min	3-8 hr	3-8 hr
	SC	10-30 min	4-10 hr	4-10 hr
NPH	SC	0.5-2 hr	6-18 hr	4-12 hr
Lente	SC	0.5-2 hr	8-20 hr	6-18 hr
Ultralente	SC	0.5-8 hr	8-24 hr	6-24 hr
PZI	SC	0.5-4 hr	NA	6-20 hr

Adapted from Feldman EC, Nelson RW: Canine and feline endocrinology and reproduction, Philadelphia, 2004, WB saunders.

Action

*insulin binds firmly to receptors with anticyclic AMP effect, increase the rate of entry of glucose, amino acids and potassium ions into most cells reverse hyperglycemia of diabetes mellitus.

Therapeutic uses: 1-in diabetes mellitus in dog 2-acetonemia in cattle and pregnancy toxemia in sheep besides the glucose therapy

Dose: The optimum dose size depends on the severity of islet dysfunction. The glucose is taken as reference adequate dose is that just eliminate or reduce glucosuria. The dose interval varies according to the type of insulin for insulin lent 6-12 hour.

Orally active hypoglycemic drugs

These are drugs which reduce the blood glucose level when given orally by stimulating insulin secretion so they have no effect in pancreatectomized animals. One group can be used safely is

Sulphonylurea (e.g. glipizide) which is

-sulphonamide with hypoglycemic effect even in normal animals.

-It may be short acting as Tolbutamide

-or long acting as Chloropropamide because it is not metabolized

-starting with 20-100 mg/kg b.wt. dosage is stabilized after 2-4 days at minimum level which exclude glucose from urine

-stimulate additional insulin production by pancreatic beta cells, increase binding of insulin to peripheral tissueinsulin receptors or enhance the cellular response to insulin

Glucagon

It is a plypeptide hormone secreted from α_2 cells of islets of langerhans. Its action on energy is opposite that of insulin. Glucagon release is enhanced by stress, starvation, hypoglycemia and exercise producing glcogenolysis, glucon-eogenesis and lipolysis. It is used therapeutically as glucagons hydrochloride for correction of insulin coma

Other drugs to control diabetes and drugs to avoid

Glucocorticoids as prednisone and dexamethasone

-mobilize glycogen stores, elevate blood glucose levels and interfere with insulin receptors, inducing hyperglycemia in a diabetic animal.

Thiazide diuretics

Phenothiazine tranquilizers such as acepromazine

ProgesteroneAdrenaline

Clinical Pharmacology

Clinical pharmacology is the application of pharmacodynamic and pharmacokinetic studies in treatment of diseased domesticated animals. These studies come from experiments performed on isolated organs or healthy laboratory animals. Clinical Pharmacology also provides scientific methods for determination of usefulness, potency and toxicity of new drugs in domesticated animal species. In the following clinical trials for treating some cases of diseased animals, chicken and fish

Case (1): Pneumonia in Cat

Case history

***A cat** of 3 kg b.wt. suffering from cough, fever, rales, dyspnea, off food. Stained film from sputum revealed presence of gram-ve rods *Bordetella bronchiseptica*

Line of treatment

1-Antimicrobial 2-Expectorant 3-Mucolytic 4-Bronchodilator 5-Antipyretic

R/ Enrofloxacin 15 mg orally every 12 h for 7 days

R/ Potassium iodide 0.3
Ammonium carbonate 0.2
Tr. Ipecac
Tr. Tolu
Infusion senega to 15 ml
M.Ft. mixture
Sig : One tea spoonful three times daily

R/ N. acetylcysteine 100 mg orally twice daily

R/ Aminophylline 15 mg orally every 12 h

R/ Acetyl salicylic acid 18 mg orally

Action and mode of action of the prescribed drugs

1-Enrofloxacin a fluoroquinolone antimicrobial, inhibit the DNA gyrase thus prevent supercoiling of DNA causing its destruction. Active against both G+ve, G-ve bacteria

2-Expectorant mixture Potassium iodide is direct expectorant, liquefy the sputum by irritation of bronchial glands during its excretion. Ammonium carbonate is an alkaline expectorant, decrease the pH and viscosity of sputum but increasing its volume and cilliary activity. It act reflexly by pharyngeal, esophageal and gastric irritation. Tr. ipecac, tr. tolu and infusion senega are nausean or emetic expectorant act by irritating the gastric mucosa

3-N. acetylcysteine Is a mucolytic, dissolve the thick sputum by breaking the disulphide bonds in the glycoprotein of sputum and facilitate its expulsion

4-Aminophylline Is a methyl xanthine derivative with broncho-dilating effect by inhibiting the phosphodiesterase enzyme in the bronchial muscle

5-Acetyl salicylic acid Is an analgesic-antipyretic. Central antipyretic acting on the thermo-regulatory center in the hypothalamus treating fever by increasing heat loss by peripheral vasodilation. Analgesic by inhibiting synthesis and release of PG_s

Case (2): Giardia in dog

Case history

***Dog** of 15 kg b.wt. showing : light colored offensive watery diarrhea, depression, anorexia, loss of weight and colic. Stool examination revealed presence of Giardia cysts or trophozoites

Line of treatment

1-Anti-giardia drug 2-Antidiarrheal drug 3-Protective

R/ Metronidazole

50 mg/kg b.wt. orally every 12 h

R/ Diphenoxylate HCl

0.2 mg/kg orally three times daily

R/ Bismuth subcarbonate

3 gm orally four times daily

Action and mode of action of the prescribed drugs

1-Metronidazole Is the drug of choice for treatment of Giardia belonging to nitromidazoles. Also effective against ameba and trichomonas. After its entry into the cell converted to toxic intermediate to the parasites

2-Diphenoxylate Is a mepridine derivative with antiparasitic activity. Stop diarrhea by anticholinergic activity

3-Bismuth subcarbonate Has protective and antisecretory effect to stop diarrhea

Case (3): Colibacillosis in calf

Case history

***A calf** 100 kg b.wt. showing : fever, colic, severe watery diarrhea, dehydration, and fecal examination revealed G-ve pathogenic E Coli

Line of treatment

1-Antimicrobial (local and systemic) 2-Antipyretic 3-Spasmolytic
4-Intestinal protective 5-Fluid therapy

R/ Cefotaxime sodium 50 mg/kg b.wt./12 h i.m.

R/ Neomycin 12 mg/kg b.wt./day orally

R/ Sodium salicylate 100 mg/kg b.wt. orally every 12 h

R/ Calcium carbonate

Bismuth carbonate	aa	0.6 gm
Gum tragacanth		0.1 gm
Chloroform water ad up to		30 ml

M.Ft. mixture

Sig : One coffee cupful three times daily

R/ Atropine sulphate 0.02 mg/kg b.wt. i.m.

R/ Fluid therapy (Rehydran) 3 liter i.v. over 24 h

Action and mode of action of the prescribed drugs

1-Cefotaxime Is a 3rd generation CSPN, active against enterobacteriaceae. It is synergistic with AMG_S. Act by inhibiting bacterial cell wall synthesis

2-Neomycin Is an AMG antibiotic, effective mainly against G-ve and also G+ve bacteria. Poorly absorbed from the GIT and thus effective locally in the gut against E. Coli. Act by inhibiting the bacterial cell protein synthesis.

3-Sodium salicylate As in case No. (1)

4-Protective mixture Ca^{++} and bismuth carbonate are protectives, adsorbents and astringents. Gum tragacanth is demulcent. Chloroform water is carminative and spasmolytic by relaxing smooth muscles and thus treat colic
5-Atropine sulphate Is a belladonna alkaloid, spasmolytic (relaxing smooth M_s) and antisecretory (decrease secretions)….thus help to stop diarrhea
6-Fluid therapy Compensate the electrolytes lost during diarrhea thus correct electrolyte imbalance

Case (4): Impaction in bull

Case history

***Bull** of 450 kg b.wt. with impaction showing : in coordination, ataxia, weakness, depression, anorexia, rumen stasis, abdominal pain, grunting and grinding of teeth, recumbent, fluid distension of rumen, acidosis & dehydration

Line of treatment

1-Antizymotic and Antifrothing agent 2-Emptying of rumen contents
3-Treat acidosis 4-Correct dehydration
5-Antihistamines 6-Adsorbent to adsorb toxins

R/ Turpentine oil 180 ml
Formalin 4 ml
Creosote 25 ml
Spiritus aminii aromaticus 30 ml
Lin seed oil 750 ml
M.Ft. solution (shake before use)
Sig : to be given directly as drench

R/ Magnesium hydroxide 450 gm dissolved in 12 L H_2O (by stomach tube)
R/ Dioctyl sodium sulphosuccinate 100 ml as drench or injected I/rumen
R/ Sodium bicarbonate 18 gm 1 % solution i.v. repeated after 24 h if needed
R/ Fluid therapy
R/ Tripelennamine 450 mg i.m.
R/ Activated charcoal 900 gm orally

Action and mode of action of the prescribed drugs

1-Antizymotic and antifrothing mixture Turpentine oil (volatile oil act as antifrothing agent). Formaline (antizymotic agent inhibiting the rumen microflora thus stopping fermentation and gas production). Spiritus amonii aromaticus (carminative by relaxing sphincter thus help expulsion of gases by bleaching). Lin seed oil (slightly irritant antifrothing agent).
2-Mg. hydroxide Antiacid used to neutralize rumen acidosis and help emptying rumen contents
3-Dioctyl Na. sulphosuccinate (Sicadine) A purgative by lowering surface tension of rumen contents thus facilitate its penetration by water and help evacuation of rumen contents
4-Na. bicarbonate Antacid to correct blood acidosis
5-Fluid therapy To correct electrolyte and fluid imbalance which may be fatal
6-Tripelennamine antihistaminic and CNS stimulant to help rapid upright standing of the recumbent animal and to help expulsion of gases and help defecation
7-Activated charcoal Adsorbent for endotoxin released by G-ve microorganisms

Case (5): Ketosis in cow

Case history

***Cow** 20 day after calving showing : loss of appetite, wasting, nervous manifestations, delirium, walking in circles straddling, crossing leg, hypoglycemia, ketonemia, ketonuria and characteristic odor of ketone in breath and milk

Line of treatment

1-Replacement of glucose 2-Anabolics and corticosteroids
3-CNS depressant to treat nervous symptoms

R/ Dextrose 50 % 500 mg i.v. and may repeated
R/ Propylene glycol 225 gm orally twice daily for 2 days followed by 110 gm daily for 2 days
R/ Dexamethasone 25 mg i.m.
R/ Trebolone acetate 120 mg single injection i.m.
R/ Chloral hydrate 30 gm orally followed by 7 gm twice daily for 5 days

Action and mode of action of the prescribed drugs

1-Dextrose -Replacement therapy to treat hypoglycemia
2-Propylene glycol -Source of glucose.
3-Dexamethasone -Stimulate gluconeogenesis on expense of oxalacetate utilization thus removing the excess of keton bodies.
4-Trebolone acetate -Anabolic steroid, increase the recovery rate by stimulating metabolism
5-Chloral hydrate -CNS depressant to treat nervous signs. Increase breakdown of starch in the rumen. Stimulate production and absorption of glucose and thus stimulate rumen fermentation with increased production of propionate which is source of energy

Case (6) : Milk fever

Case history

***Milk fever in buffalo** of 450 kg b.wt. one day of calving showing : lowered body temperature (36 C°), depression, paralysis and lateral recumbency with head and neck deviated to one side

Line of treatment

*Replacement therapy to treat hypocalcaemia and hypoglycemia

R/ Calcium borogluconate 25 % 800 ml by slow i.v. infusion
R/ Glucose 40 % 500 ml i.v. infusion
R/ Sodium acid phosphate 15 % 200 ml i.v.
R/ Magnesium sulphate 15 % 300 ml

Action and mode of action of the prescribed drugs

1-Ca. borogluconate A drug of choice to treat hypocalcaemia of milk fever to restore Ca level to normal level so the skeletal muscle contraction return to normal
2-Glucose -Source of energy and treat hypoglycemia
3-Na acid phosphate -Source of phosphorous essential for many metabolic processes including energy
4-Mg SO_4 -Essential for normal muscle tone

Case (7) : Parasitic diarrhea in horse

Case history

***Horse 300 kg b.wt. showing :** chronic diarrhea, microcytic anaemia, anorexia, intestinal colic. Stool examination revealed heavy strongylus infestation

Line of treatment

1-Antinematodal drug 2-Astringent mixture 3-Haematinic

R/ Phenothiazine 30 i.u.
Piperazine adepate 30 gm
Aqua ad 1000 ml
M.Ft. suspension, send 3000 ml
Sig : One liter daily for 3 days

R/ Calcium carbonate 120 gm
Tr. catechu 150 ml
Kaolin (aliminium trisilicate) 120 gm
Spiritus chloroformi 150 ml
Aqua 500 ml
M.Ft. mist.
Sig : 150 ml three times daily in 500 ml flour gruel

R/ Gentiana 120 gm
Nux vomica 15 gm
Sodium bicarbonate 120 gm
M.Ft. pulv. Divide into 8 doses
Sig : One sachet three times daily before meal

R/ Atropine sulphate 15 mg 10 % s/c

R/ Ferrous sulphate 10 gm
Liquorice
Treacle aa Q.s
M.Ft. electuary
Sig : to be smeared once daily

Action and mode of action of the prescribed drugs

1-Phenothiazine Nematocide against strongylus, tricostrongylus, stomach and other round worms in cattle, sheep, horses and poultry. Act by inhibiting glycolysis and egg laying capacity of worms. It may be lead to Hb uria, jaundice and color urine red

2-Piperazine Nematocide for small and large animals. Against ascarids and oxyuris in hoses. Has curare like action (paralyze the worms which are expelled by peristalsis

3-Astringent mixture i-Ca carbonate (astringent and adsorbent) ii-Tr. catechu (release tannate which is astringent by ppt. of proteins) iii-Kaolin (astringent and adsorbent) iv-Spiritus chloroformi (flavouring agent and treat colic i.e. SM relaxant)

4-Stomachic powder *Gentian (bitter stomachic, reflexly stimulate sensory nerve ending of taste buds and thus increase saliva and gastric secretion) *Nux vomica (contain strychnine which is stomachic)*Na bicarbonate (chemical antacid locally and systemically)

5-Atropine sulphate as in the case No. (3)

6-Haematinic electuary *Ferrous sulphate (source of iron, astringent, given after meals to avoid irritation.) *Liquorice and treacle (vehicles)

Case (8) : Rumenotomy

Case history

***Cow** 200 kg b.wt. with traumatic reticulitis

Line of treatment

*Rumenotomy under local anesthesia using :

1-Tranquilizer 2-Muscle relaxant 3-Local infiltration anesthesia
4-Antiseptic 5-Antibiotic to prevent secondary infection

R/ Xylazine HCl (Rumpon) 0.06 i.m.
R/ D-tubocurarine 0.2
R/ Procaine HCl (Novocaine 2 %) 20
R/ Citrimide (Cetavlon)
R/ Liquor iodi firtis B.P. 5 %
R/ Procaine penicillin 1000 i.u.
Streptomycin HCl 2
Aqua dis. Ad 10 i.m.
One daily for 5 days

Action and mode of action of the prescribed drugs

1-Xylazine -A neuroleptic tranquilizer with a sedative, analgesic and muscle relaxant effect of central origin. Its analgesic effect lasts for 15-30 minutes while its hypnotic effect lasts for 1-2 h. It causes no initial excitation but may lead to respiratory depression, bradycardia and prolonged hypotension

2-Tubocurarine -A competitive muscle relaxant indicated for skeletal muscle relaxation controlling the animal and help surgical interference after local anesthesia

3-Procaine HCl 2 % -Induce paravertebral local anesthesia involving the surgical area of rumenotomy. It is better to be accompanied with adrenaline 1/10000 to prolong its action and inhibit bleeding (ensuring bloodless operation)

4-Citrimide -A quaternary ammonium compound for cleaning and defattening area of operation and to become ready (prepare it) for antisepsis and sterilization

5-Liquid iodi fortis 5 % -A sterilizing agent for the area of surgery by its contents of iodine (germicide) and alcohol (dehydrate bacteria)

6-Antibiotics -Procaine penicillin…long acting PCN for 24 h. Act by inhibiting bacterial cell wall synthesis. -Streptomycin…..Bactericidal AMG, effective mainly against G-ve bacteria by inhibiting bacterial cell protein synthesis. May lead to nephro-, hepato-, auto- and neuro-toxicity.

-The 2 antibiotics act synergistically to prevent infection of surgical area

Case (9) : Cesarean section

Case history

***Cow** 300 kg b.wt., late pregnant, dystokia, "breech presentation"

Line of treatment

*Cesarean section under neuroleptanalgesia using :

1-Tranquilizer 2-Muscle relaxant 3-Local infiltration anesthesia
4-Antiseptic 5-Antibiotic to prevent secondary infection

R/ Xylazine HCl (Rumpon) 0.1 i.m.
R/ Etorphine 0.1 i.m.
R/ Decamethonium 60 mg i.v.
R/ Procaine HCl (Novocaine 2 %) epidural

R/ Citrimide (Cetavlon)
R/ Liquor iodi firtis (B.P.) 5 %
R/ Tetracycline HCl 1.5 i.m.
Daily for 5 days

Action and mode of action of the prescribed drugs

1-Xylazine -As in case No. (8)
2-Etorphine -A powerful analgesic (1000 times more than morphine). Indicated with xylazine to induce neuroleptanalgesia. It may increase the heart rate and blood pressure blocking the adverse effects of xylazine in cattle
3-Decamethonium -A non competitive neuromuscular blocker causing skeletal muscle relaxation controlling the animal and help surgical interference with neuroleptanalgesia
4-Procaine HCl 2 % -As in case No. (8). Epidurally may lead to respiratory depression which can be counteracted by medullary analeptics as ethamivan
4-Citrimide -As in case No. (8)
5-Liquid iodi fortis 5 % -As in case No. (8)
6-Tetracycline HCl -A broad spectrum antibiotic. Bacteriostatic against G+ve and G-ve bacteria. Act by inhibiting the bacterial cell protein synthesis. It is widely distributed in the body crossing barriers and excreted in urine and bile. Precipitated in bone and teeth.

Case (10) : Retained placenta

Case history

***Buffalo** 350 kg b.wt. showing : post partum hemorrhage, retained placenta, metritis, fever, abdominal pain and developing milk fever

Line of treatment

1-Ecobolic 2-Spasmolytic 3-Antiseptic 4-Calcium to treat milk fever

R/ Syntocinon 30 mg i.m.
R/ Stilbosterol dipropionate 30 mg i.m.
R/ Methyl ergometrine (Methergin) 10 mg i.m.
R/ Atropine sulphate 1 % 30 gm i.m.
R/ Oxytetracycline HCl tablets locally in the uterus
R/ Tetracycline 1 i.m. daily for 5 days
R/ Calcium borogluconate 20 % 500 ml i.v. infusion

Action and mode of action of the prescribed drugs

1-Syntocinon -Synthetic oxytocin to sensitize the uterus for the ecobolic effect of stilbosterol to get rid off the placenta. Also stimulate uterine contraction and help let down of milk by contracting milk acini of mammary gland
2-Stilbosterol -Synthetic estrogen stimulate contraction of the pre-sensitized uterus by oxytocin to help expulsion of retained placenta
3-Methyl ergometrine -Uterine stimulant ergot alkaloid. Help rapid involution of uterus and contract the blood vessels after expulsion of fetus, fetal membranes and placenta thus stop the postpartum hemorrhage
4-Acriflavine -Acridine disinfectant dye. Inhibit the synthetic processes of M.O. Safe to be used internally as uterine wash after expulsion of retained placenta
5-Atropine sulphate treat colicy pain that accompany metritis and retained placenta
6-Oxytetracycline HCl tablets -Broad spectrum antibiotic applied locally in the uterus. Act by inhibiting bacterial cell protein synthesis. Bacteriostatic effect against G+ve and G-ve micro-organisms that induce metritis

7-Tetracycline HCl -Injected to induce systemic effect. Act synergistically with locally applied TTC

8-Ca^{++} borogluconate -Ca^{++} gluconate + boric acid. Correct sudden drop in Ca^{++} level of heavy milking buffalo cow after calving and exhaustion of Ca^{++} by fetal bone development.

Case (11) : Organophosphate toxicity

Case history

***Bull** 350 kg b.wt. showing : diarrhea, salivation, bradycardia, hypotension and paralysis

Line of treatment

1-Muscarinic blocker 2-Enzyme re-activator 3-Anticonvulsant
4-Purgative 5-Diuretic mixture

R/ Atropine sulphate 1 % 30 mg s/c
R/ Pralidoxime (2-PAM) 10 ml i.m.
R/ Pentobarbitone Na (luminal) 200 i.v.
R/ Mg. SO_4 500 gm
Aqua ad 1000 ml
M.Ft. solution
Sig : One drench

R/ Potassium citrate 75 gm
Potassium nitrate 75 gm
Spiritus ether nitrosi 150 ml
Aqua ad 455 ml
M.Ft. solution
Sig : 200 ml to be given orally as drench every 4 h

Action and mode of action of the prescribed drugs

1-Atropine sulphate -Block muscarinic effects of Ach (bradycardia, excess secretions, hypotension)

2-Pralidoxime (2-PAM) -Antidote for OP_s toxicity. AChE re-activator and prevent new complexes to be formed between OP_s and AChE

3-Pentobarbitone Na (luminal) -Short acting barbiturate to block the excitatory effects result from the central ganglionic stimulation of nicotinic receptors in the brain by excess Ach. Also to block the depolarizing neuromuscular blocking effect of Ach and paralysis of diaphragmatic muscles which ended by asphyxia and death

4-Mg. SO_4 -Bulk forming purgative, increase the osmotic tension of intestinal lumen, thus prevent absorption of water from intestinal lumen (retain water). Also attract (draw) water from the surrounding tissues and blood into the intestinal lumen. Thus increase the bulk of intestinal contents leading to intestinal distension and increased peristaltic activity….."stimulate defecation" and expulsion of the OP_s that not yet absorbed. Also Mg. ions stimulate release of cholecystokinin (CCK) hormone which increase the peristaltic activity and fluid secretion

5-Diuretic mixture

-Act synergistically with purgative to expel OP_s through urine. Potassium citrate and nitrate are osmotic diuretics inhibit the renal tubular re-absorption of toxin causing its renal expulsion

Case (12) : Pyelonephritis in cow

Case history

***Cow** 300 kg b.wt. showing : fever and colic of uro-genital origin
*Rectal examination revealed thickening of wall of urinary bladder and ureter, enlarged kidney with loss of lobulation
*Urine analysis revealed presence of blood and pus and G+ve *Corynebacterium renale*

Line of treatment

1-Antimicrobial for infection 2-Spasmolytic for colic 3-Antipyretic for fever 4-Diuretic
R/ Penicillin procaine 60 i.u./kg b.wt. i.m.
R/ Atropine sulphate 1 % 30 gm i.m.
R/ Sodium salicylate 30 gm
R/ Ammonium chloride 100 mg/kg b.wt. twice daily orally

Action and mode of action of the prescribed drugs

1-PCN-procaine -Bactericidal antibiotic against C. renale by inhibiting cell wall synthesis
2-Atropine sulphate -In case No. (3)
3-Sodium salicylate -In case No. (3)
4-Ammonium chloride -Expectorant and diuretic. Also urinary acidifier, change the urine pH to acidic nature to become unfavorable media for growth of C. renale

Case (13) : Coccidiosis in chicken

Case history

***Chickens** 3 weeks old showing : brown and bloody diarrhea
*PM finding of dead chickens revealed presence of coccidiosis

Line of treatment

1-Anticoccidial 2-Coagulant 3-Growth epithelial factor
R/ Amprolium HCl
Sulphaquinoxaline equal amounts
One gm/L drinking water for 5 days
R/ Vitamin K_1 0.002 gm/kg food
To be mixed with ration for 5 days
R/ AD_3E 100 i.u. 40 mg/ml
25 ml/100 L for 3 days

Action and mode of action of the prescribed drugs

1-Anticoccidial mixure -Amprolium HCl…is a vitamin B_1 (thiamin) antagonist depriving the coccidian from an essential factor for its growth. Sulphaquinoxaline…is a coccidiostatic by competing with PABA which is essential for synthesis of folic acid which is essential for coccidial growth. Both act synergistically to protect against and to treat coccidian. Adverse effects are thiamine deficiency and crystalluria and depression of egg production
2-Vitamin K_1 -A lipid soluble vitamin essential for blood clotting. Block the caecal bleeding caused by coccidian
3-AD_3E -Vitamin A…growth factor and epithelial cell protective. Vitamin D_3…essential for bone growth and precipitate Ca and phosphate in bones. Vitamin E….essential for growth and reproductive capacity
*This vitamin mixture generally increase the immune status of chickens to resist infection.

Drug Toxicology

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Definitions

*Toxicology: Means science of poisons including their source, character, toxic effect, treatment of their untoward effects and detection of these poisons.

*A-poison: is any substance which, when ingested, inhaled, absorbed, or when applied to, injected into, or developed within the body, in relatively small amounts, or in farley amounts (drug) may cause damage to body structure or disturbance of function through its chemical action.

Classification of drug toxicology

I-General toxicology

II-Special toxicology (1-Metalloids 2-plant toxins 3-Animal toxins).

Causes of toxicity

1-Drugs when given in over dosage are toxic. 2-Some drugs when given for a long period have toxic effects. 3-Animal grazing on green fooder sprayed with insecticides, pesticides or herbicides. 4-Animal grazing on pasture heavily infested with poisonous plants.

Fate of poisons in the body

When the administration of poisons per os occurs, it is partly absorped. Other parts, the body get rid off by vomiting or diarrhea. After absorption, the poison passes to the liver and then passes into the general circulation aand exerts its action on the particular organs and is later destroyed in the tissues and eliminated from the body by means of kidney or through perispiration, milk and other natural secretion. Certain poisons, excreted through the bile, pass back from the intestine reabsorption and reexcretion takes place from and into the intestinal tract. Volatile poisons are excreted through lungs.

Factors Modifying the effect of poisons
(Factors affecting toxic response)

1-Amount of the drug:….. Larger amounts are more toxic.
2-Form of the drug:….. Liquids are more toxic than solids.
3-Route of administration:….Parenterally, toxicity is hastened.
4-Solubility of the drug:…. hastens the probability of toxicity.
5-Condition of the stomach:…. Empty stomach exaggerates toxicity.
6-Age and health:…… younger and debilitated are liable.
7-Idiosyncracy:…… predisposes for toxicity by low doses.
8-Addiction and habit:…… improves tolerance to toxins.
9-Accumulation:……..predisposes for toxicity by low doses.

10-Species of the animal:.....certain species are sensitive, others are insensitive to certain toxins.

Classification of poisons

1-According to their source:

A-Organic poisons:

a-plant origin e.g. atropine, morphine and digitoxin.

b-Animal origin: e.g. snake venom and cantheridin.

c-Synthetic origin e.g. Carbon tetrachloride, chloroform and Sulphonamides.

B-Inorganic poisons:

a-Acids, e.g. conc. Sulphuric and nitric acids.

b-Alkalies, e.g. conc. Solution of sodium and ammonium OH.

c-Metallic, e.g. salts of mercury and lead. etc,

d-Non metals. eg. Salts of bromides and iodides etc.

2-According to the degree of toxicity:

A-Strong poisons: Induce intense symptoms and may lead to death, e.g.: salts of arsenic and cyanides.

B-Weak poisons: The symptoms less severe and do not lead to death (Alcohol and copper salts).

3-According to their action:

A-Local actions: such as concentrated acids and alkalies when contact with skin and mucous membrane.

B-General poisons: Induce their effects after absorption in the blood (morphine, strychnine and arsenic)

C-Mixed poisons: That poisons induced their effects locally and after its absorption as tartar emetic.

4-According to their site of action:

A-Poisons of central nervous system (morphine, chloroform and strychnine).

B-Poisons of autonomic nervous system (atropine and methacholine).

C-Poisons of circulatory system (digitoxin and strophanthin)

D-Poisons of urinary system (sulphanilamide and cantharidin)

E-Poisons of respiratory system (carbon dioxide and morphine)

5-According to their mode of action:

A-Corrosives and irritant:that cause ulcers in the skin and mucous membrane. e.g conc. acids and conc. alkalis,

B-Narcotic poisons: that drugs cause depression to brain. e.g chloroform, chloral hydrate bromides and barbiturates.

C-Stimulant poisons: that cause more stimulation. e.g strychnine on spinal cord, caffeine on brain.

D-Depressant poisons: drugs which induce more depressant effect, e.g morphine on brain, atropine on parasympathetic nervous system and bromide on spinal cord

Diagnosis of poisoning

1-Symptoms of toxicity on a large number of animals. There are no general symptoms for all poisons that leads to diagnosis.
2-Presence of poisonous plant seeds in the vomitous.
3-The odor of respiration helps in diagnosis.
4-The color of urine.e.g phenothiazine changes the color of urine to red and phenol to green color.

General treatment of poisoning

A-Removal of poisons

1-Gastric lavage (stomach wash):

This should be done as early as possible to remove any poison still present in the stomach. Don't wash stomach in corrosive acid or caustic alkali poisoning because the esophagus or stomach can easily be ruptured by the use of the stomach tube. Notice that drugs as morphine and arsenic are excreted into the stomach, hence, lavage is indicated in such cases, even though these drugs were given hypodermically.

2-Emetics:

These should be administered to animals that vomit when stomach lavage is not possible. Any of the following emetics may be used for dogs:

i-Sodium chloride solution (one teaspoonful) in half glass of warm water.
ii-Coppersulphate solution (one gram in half glass of warm water.
iii-ApomorphineHCl (1-7 mg) injected hypodermically.

N.B: Apomorphine may not act in cases of great depression of the vomiting center as in narcotic poisoning. In poisoning with drugs which anaesthetize the stomach, emetics may fail to act, e.g carbolic acid. Do not use emetics in corrosive acids or caustic alkali poisoning.

3-Aid excretion:

By stimulating kidneys, bowels and skin as following:

a-Diuretics: give water by mouth; If the potient is conscious and could swallow, caffeine, theobromine or organic salts such as potassium acetate citrate and tartrate by mouth, normal saline may be given by subcutaneous or intravenous injections and any other diuretics as lasix.

b-Purgatives: saline purgatives are preferred, also enema especially in poisoning by heavy metals and morphine (which is excreted in the large intestine). In equines to produce a rapid evacuation through the large intestine eserine, pilocorpine and arecholine are usually given subcutaneously.

c-Diaphoretics:e.gpilocarpine may be used for dogs.

B-Administration of antidote

1-Symptomatic antidote:

These are substances given to prevent the general symptoms to appear on the animal e.g…..Anti-emetics for vomiting, Astringents in diarrhea, Stimulants in depression, Artificial respiration in collapse, C.N.S depressants in excitation and convulsions.

**If the poison is unknown give the universal antidote. e.g for dog 15 gram in a half glass warm water. Universal antidote consists of: two parts activated powdered charcoal, one part tannic acid and one part of magnesium oxide.

2-Chemical antidote:

Which renders the poison harmless by precipitation or decomposition or chemical antagonism.e.g….Iodine by starch, Corrosive acids (Carbolic acid) by weak alkalis, caustic alkalis as causting soda by weak acids as dilute acetic acid, vinegar or ascorbic acid.

3-Pharmacological antidote:

that counteracts the effects of poison. e.g… physostigmine by atropine and strychnine by barbiturates

4-Specific antidote:

e.g….. for strychnine give mephensin for morphine give nallorphine.

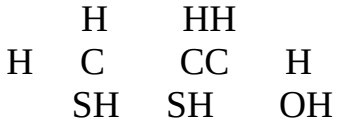
N.B: If the specific chemical antagonist is not available, large quantities of milk and eggs may be used (mechanical antidote) in certain poisons taken orally.

Chelating agents

Chelating agents are drugs which bind with heavy metals forming a poorly dissociable complexes known as chelates. Chelating agents of clinical use must have a lower affinity for calcium than for the heavy metal otherwise it will produce hypocalcaemia,

1-Dimercaprol (BAL):

British anti lewisite (Dimercaptopropanol) provides two thiol groups on adjacent carbon atoms with which arsenic, mercury and cadmium combine to form chelates, as these have an affinity to the thiol group in SH enzymes. BAL can be used to treat poisoning with these heavy metals. Dimercaprol itself is oxidized in the tissues, thus releasing the metal from chelate, Thus a continuous supply of BAL must be given. BAL must be supplemented rapidly in poisoning as the reactivation of SH enzymes depends on the length of time since their inactivation. Dimercaprolitslf is toxic if in large doses resulting in C.N.S, symptoms as tremors and convulsions, vomiting and damage of the capillaries may occur.



Dimercaprol

2-Penicillamine (Dimethyl cysteine):

It is an orally administered chelating agent, it resembles BAL in containing SH groups, it is prepared by the hydrolysis of penicillin. It chelates copper mainly and also mercury, zinc and lead thus allows the safe excretion of these metals in urine. Penicillamine can cause pyridoxine deficiency and prevents the formation of calculi in cystinurea.

3-Sodium calcium edentate: (B.Vet.C):

It is the Ca chelate of disodium ethylene diaminetetracetic acid. It forms a stable soluble metallic chelate with divalent metallic ions which have a higher affinity for chelation than calcium. It is mainly used for lead poisoning where lead bind to the disodium salt more strongly. Leaving Ca. It can be injected I.V.33 mg/Lb/day, given in divided doses. Lead appears in urine as the chelate not free ions. Sod. Ca. edentate is relatively non toxic. It is also used as a chelating agent for radioactive metals, uranium and plutonium.

4-Desferrioxamine:

A strong chelating agent for ferric iron and it is capable of removing it from certain physiological chelates as ferritin and transferring, but not from haemoglobin or the cytochrome oxidase enzyme. It is given Parenterally. Sodium ferrocyanide is a chelator of iron given orally.

SPECIAL DRUG TOXICOLOGY

I-Metallic poisoning

1-Lead poisoning

Lead poisoning occurs in cattle and dogs from administration of lead sulphate, acetate and arsenate.

Absorption and excretion: after oral administration of lead it is distributed to all tissues of the body especially liver, muscles, bones and kidneys. It is excreted
slowly with urine and milk.

*Lead induce its effect by inhibiting the SH group and interaction with carboxydiphosphoryl groups.

Symptoms

a-acute poisoning: convulsions, salivation, abdominal pain. Tetany and death.
b-Chronic poisoning: (specially in horses) loss of weight, swollen knees, discolouration in the gums due to deposition of lead sulphide and sometimes aneamia occur.

Treatment:

a-In acute poisoning: Gastric lavage saline purgatives as magnesium sulphate. Emetics (sodium sulphate) or white egg or tannic acid to prevent more absorption from intestine.
b-In chronic poisoning: C.N.S depressants as barbiturates & calcium disodium edentate as a chelating agent. Duiretics help in the excretion of lead with urine.

2-Mercury poisoning

Mercury poisoning occurs during the treatment with mercuric compounds (mercuric iodide, and mercuric chloride) in veterinary practice.

Absorption and excretion: Mercuric chloride is rapidly absorped from gastrointestinal tract; it is absorped from the skin (ointment) or washing the wounds with mercuric chloride. The excretion of mercury is slowly via urine, faeces, saliva and milk. It is stored in the liver, kidneys and tissues. Mercury inactivates the SH group enzymes and interferes with cell metabolism.

Symptoms: Dogs and cats are more sensitive for mercury poisoning than other animals.
a-Acute poisoning: Abdominal colic and diarrhea with excessive salivation, difficulty in swallowing with stomatitis, decreased urination and after one week anurea occur. Sometines in cattle with mercury poisoning, colic, paralysis and decrease body trmperature are the only symptome in acute case.
b-Chronic poisoning: Excessive salivation, gum ulceration, disturbance in the digestive and urinary systems, decreased body weight and anaemia.

Treatment: Gastric lavage, White egg orally to form mercury albuminate and removed by gastric lavage, give diuretics and give chelating agent as BAL or Penicillamine.

3-Arsenic poisoning

The arsenical salts are widely used in veterinary therapeutics and as insecticides, so the poisoning with arsenic occurs in field animals

Absorption and excretion:

The arsenical salts especially inorganic are absorped from intestine and from the skin and wounds. Aresnic stored in the liver, clowes, bones and different tissues. The excretion of arsenic is with urine and faeces, sweat and milk. It appears in the urine for two months after last dose.

Symptoms:

a-Acute: It appears after 3-10 hours after administration and the symptoms appear in the form of abdominal colic, excessive salivation, vomition diarrhea, cardiac arrhythmia, sluggish motion, decrease in the amount of urine, stupor and death.
b-Chronic: Decrease in the body weight, dry skin, redness of mucous membrane and cardiac arrhythmia.
Treatment: In acute poisoning; Gastric lavage with warm water and saline purgatives and give ferric oxide. Give BAL and diuretics.

4-Copper poisoning

Copper poisoning occurs mainly in sheep due to the pullotion of herbs and water with copper sulphate.

Symptoms:
a-Acute: severe colic with mucoid diarrhea, excessive salivation and colouredvomition, convulsions followed by stupor and death.
b-Chronic: Debility of animals and anemia.

Treatment:
Give BAL by injections to form a compound with copper, rapidly excreted.

5-Cyanide poisoning

The poisoning with cyanide is due to uses of its salts as herbicide fertilizers for lands as well as its presence in some plants. Cattle are susceptible for poisoning than horses.

Symptoms: Excessive salivation with foaming around the mouth, convulsions, stupor end with death due to respiratory failure.

Treatment: Sodium nitrate administered intravenously to form cyanomethoemoglobin, then inject the animal with sodium thiosulphat for changing this compound to be harmless and easily excreted.

6-Selenium poisoning

Selenium present in some plants and its toxicity resulted to animals fed on plants containing it.

Absorption and excretion: Selenium is absorped from gastrointestinal tract. It is distributed in all bodyincluding placenta and foetus. It is stored in liver, spleen and kidney. It is excreted in the urine.

Symptoms:
A. acute: abdominal pain, rapid pluse, difficult respiration end with death.
B. Subacute: Debility of animals, difficult vision and swallowing, convulsions ending with paralysis, stupor and death.
C.Chronic: loss of hair(tail & neck in horses), dry skin end with lameness.

Treatment:
Give parabromobenzene, don't give BAL, because it ↑ toxicity of selenium.

Insecticide poisoning

The insecticides are divided into old ones e.g……lead arsenate, zinc arsenate, nicotine, kerosene, cyanide and carbon tetrachloride and modern insecticides, which are divided into:

1-Chlorinated hydrocarbons

e.g…D.D.T; methoxychlor, lendane, Aldrine, dieldrin and chlordane. Some of chlorinated hydrocarbons disturb the metabolism of fat by increasing the oxygen consumption. Other compounds affect the calcium in the nerve tissues and lead to convulsion. Some of these compounds affect the enzymatic system of the body inducing their toxicity.

Absorption and excretion:

Some of the chlorinated hydrocarbons are absorbed from the intestine, others from intact skin, stored in the fat of the body after their absorption. D.D.T is excreted in the milk; some chlorinated hydrocarbons are excreted from the intestine.

Symptoms:

1-D.D.T &Gamexan: The animals die as a result from depression of C.N.S and resiperatory failure.

2-Other chlorinated hydrocarbons: Convulsion, excessive salivation, vomition ending with shivering and muscle tetany.

Treatment:

a-Gastric lavage emetics, saline purgatives. If the animal did not die within two days it will recover.

b-Give sedatives (barbiturates and chloral hydrate).

c-Give calcium borogluconate and glucose.

2-Organic phosphorus compounds

e.g….Malathion, parathion, Diazinon and Dipterex.

Organic phosphorus compounds induce their toxicity forming fixed compounds with cholinesterase enzyme, so the acetylcholine increases in the body with demyelination of spinal cord and nerve endings.

Absorption and distribution: Absorption occurs from intestine, lungs and skin while the excretion occurs with faeces, bile and rarely with milk.

Treatment: Gastric lavage, Give atropine 0.5 mg/kg b.wt. every 4 h for one or two days, Give 2 PAM pralidoxine SC for dephosphorylation of cholinesterase.

II-poisons of plant origin

1-Atropine poisoning

Atropine poisoning occurs when animals feed on seeds of ateopa belladonna plants that contains atropine-Also poisons induced by injections with large doses of atropine. Cats and dogs are highly affected more than horses while cattle and rabbits are little affected with atropine.

Absorption and excretion: Atropine remains for a short time in the tissues after its absorption. Large amounts of atropine are oxidized in the

liver and muscles, The remaining part of atropine is excreted as it is in the urine.

Symptoms: Acute symptoms of atropine poisoning are respiratory failure, dry mouth, dilated eye pupil, increase heart beats shallow respiration, convulsions then the animal cannot move and die from respiratory failure.

Treatment: Gastric lavage with diluted solution of potassium permanganate and emetics, Give sedatives (choral hydrate and a barbiturate) and Give antidote for atropine (eserine).

2-Strychnine poisoning

Strychnine poisoning occur when the animals take nux vomica per os or parenteral with toxic doses.Dogs and cats are sensitive than horses and cattle for strychnine.

Absorption and excretion: Strychnine has a cumulative effect for its slow excretion, it is absorped rapidly from the mucous membrane or from site of injections. It is absorbed slowly from the skin. It appears in the saliva after few hours.

Symptoms of poisoning: The symptoms begin with shevering then tetany of muscles of neck and jaw. Colonic convulsions of the body with arched back for a period long or short according to the dose of strychnine, Later relaxation of the muscles of thebody. The animals die from respiratory failure resulting from contraction of diaphragmatic and intercostals muscles leading to asphyxia.

Treatment: Give the animal ether or chloroform or chloral hydrate to stop convulsions, Separate the animals in a calm dark stable and give Nembutal and Give specific antidote (mephenesin).

3-Nicotine poisoning

Poisoning with nicotine is rare in animals. It is absorbed from lungs and excreted with urine, saliva and in expired air.

Symptoms: Inflammation of throat, rapid respiration then slow. Constricted eye pupil. Shivering and convulsions of muscles then relaxed. The animal lie in the ground in stupor and die from asphyxia.

Treatment: Give gastric lavage with water and tannic acid. Give respiratory stimulants.

4-Morphine poisoning

Morphine is obtained from papaversomniferum fruit. Morphine differs in, its effect between stimulation and depression of the brain in animals according to the anatomical and physiological variation among animals. Morphine poisoning is rare in animals.

Absorption: morphine is rapidly absorbed either taken orally or by injection. It is excreted in the stomach and in the urine after oxidation in the blood.

Symptoms:

a-In cattle and horse: dilated eye pupil, difficult respiration then the animal stuppred (constricted eye pupil, slow respiration, indigestion and bloated).
b-In dogs: constricted eye pupil, disturbance of respiration, then the animals stuppored and death occurs from arrest of respiration.
Treatment: Gastric lavage with water or diluted solution of potassium permanganate or tannic acid. Saline purgatives (magnesium sulphate). Respiratory stimulants (cardiazole) inspired carbogen for animals. Antidote (nallorphine).

5-Digitoxin poisoning

Digitoxin is present in fox gloves (leaves and seeds).Cattle and sheep resist its toxicity more than other animals if taken orally. On the other hand its administration by injections is equal in its toxicity to all animals.
Absorption and excretion: Digitoxin is easily absorbed form intestine. Its effect appcared after 6 hours of administration.Digitoxin is excreted with urine for 50 days after last administration.
Symptoms: Vomition, diarrhea, difficult respiration,weak heart beats and arrhythmia and the animal diesfrom cardiac arrest
Treatment: Gastric lavage. Saline purgative (atropine).Specific antidote.

6-Ergotoxine poisoning

Poisoning occurs if animals fed on plant or seeds infested with Clavicepspurpurae fungi that contain ergotoxine.
Symptoms: loss of sensation in end parts (tail, ear and clawes) leading to dry gangarene (the blood vessels constrict preventing the blood for reaching this areas so gangarene occur). Clonic convulsions, vomiting & diarrhea may occur.
Treatment: Gastric lavage. Give amyl nitrite. Give anticonvulsant

7-Aflatoxin

A toxin from sporidesmun which results in in hepatotoxicity. This fungus grows on dead tissues and its spores infect growing sheep resulting in great losses. It result in kidney irritation, liver degeneration and fibrosis of bile ducts, photosensitization due to failure of excretion of chlorophyll is induced.
Aflatoxin B1: A toxin in trace amounts in food, produced by asperigellusmoulds, invading food stuffs as maize or beans when dried in the field). It is very potent toxin in trace amounts. Species differ in their susceptibility, they also differ according to age, sex and enzymatic activity in different tissues. Ducks are very susceptible. Cattle show symptoms of blindness, circuling and die in 2 days. Chronic toxicity of aflatoxinresult in carcinoma of the liver and kidney. Aflatoxin is hydrolyzed in the liver resulting in toxicity by affecting the DNA inhibiting protein synthesis.

Tricothrecene: It is a mycotoxin resulting in severe poisoning and damage in man and animals. It is very irritant resulting in necrosis and necrotic ulcers in the esophagus and result in a toxic effect on blood forming tissues with anemia, fever and skin rashs. These toxins are very stable to heat.

III-Poisons of animals origin

A-Snake Venum

Snakes and vipers secretes their poisons from their salivary glands. Snake venum contains neurotoxin, that could affect the nervous tissues, respiratory centers and blood vessels. Moreover, vipersvenum contains substances affecting the blood and circulatory system.

Symptoms of poisoning:

a-Snakevenum: local symptoms in the site of bite (severe pain, inflammation and swelling). General symptoms (vomiting, excessive salivation, constricted eye pupil, decrease in respiratory rate, paralysis of respiratory muscles ending with death in few minutes)

b-Vipersvenum: local symptoms (severe pain, swelling at the site of bite and surrounded by bleeding under the skin). General symptoms (like histamine symptoms…slow pulse rate, dilate eye pupil, heart failure ending with death).

Treatment:

1-ligate above the bite in the direction of the heart at once

2-get rid off the snake venum or vipers venum by bleeding the site of bite before absorption

3-wash the site of bite with 10 % solution potassium permanganate to oxidize the poison.

4-inject serum containing polyantivenum I/V

5-artificial respiration or respiratory stimulants (in case of snake venum) and adrenaline or atropine (in case of vipersvenum).

*Snake venoms contain complex mixtures of various organic materials (proteins, peptides, amino acids and other compounds). Enzymes are the major toxic components of snake venoms phospholipase A2 activity is basic to the action of many of the toxins in snake venoms. Pharmacologically phospholipase A2 may have neurotoxic, cytotoxic and anticoagulants activities cytotoxic phospholipase A2 from lysolipids that act like detergents in lysing cells, causing necrosis of muscle tissue (mycotoxins), As anticoagulants phospholipase A2 elminate the procoagulant phospholipids before blood clotting factors can be activated and begin amplification of the clotting.

General management of snake bite in animals

A-First aid: call a veterinarian…the animal owner should keep the animal as quiet as possible and seek medical assistance. If the victim can

not be transported to a medical facility within an hour, a tourniquet should be applied proximal to the bite and loosened for 1 min every 10 min. the tourniquet should not be removed until 3 min after antivenin therapy has begun.

B-Hospital care: if venomous snake bite is suspected, a thorough physical examination should be conducted. Blood samples should be collected for hematology and serum chemistry studies. in the case of small companion animals, an intravenous catheter should so that infusion of antivenin may be begin immediately if signs of envenomation appear. Antivenin should be administered only if the signs of envenomation appear as described for human. Antivenin is the only specific therapy for snake envenomation of animals.

B-Scorpion poisons

Scorpion venom is complex, consisting of a mixture of many pharmacologically active, neurotoxic proteins (as many as 16 different proteins in a single venom). Some proteins are enzymes, others not. Phospholipase A2 is commonly present in the venom of scorpions, while other enzymes such as hyaluronidase, phosphomonoesterase, acetylcholinesterase and others may be found in the venom of some species but not in others. Scorpion poisons are secreted from glands at the end of the tail. This poison is like the snake venom but its effect is less.

Symptoms:

Vomiting, increased sweat, convulsion followed by paralysis in voluntary muscles especially respiratory muscles ending with death.

Treatment:

1-ligate at once above the site of bite in the direction of the heart

2-get rid off the poison by bleeding before its absorption

3-wash the site of bite with 10 % solution potassium permanganate to oxidize the poison.

4-inject adrenaline and local anesthesia (novocaine) around the site of bite

5-inject the animal with serum containing antiscorpion poison.

APPROACH TO FISH PHARMACOLOGY

Major cultured species

1- Fresh water fish:
2- Marine water fish:
3- Food fish:
- Carp fresh water fish, Trout fresh water fish, Cat fish and Tilapia

4- Warm water food fish:
- Fish grow vigorously at high temperature greater than 15 ^{o}C
- **Ex.** Channel cat fish, Tilapias

5- Cold water food fish
- Fish grow vigorously at low temperature generally less than 15 ^{o}C
- **Ex.** Salmon, Trout, Rainbow trout, Atlantic salmon, Brown trout, various pacific salmon

ANTIBACTERIAL DRUGS IN FISH FARMS (APPLICATION AND EFFECTS)

- A wide range of chemicals are used in aquaculture, including anti-bacterials, pesticides, hormones, anesthetics, various pigments, minerals and vitamins, although not all of them are antibacterial agents
- Antibacterial chemotherapy has been applied in aquaculture for over 60 years
- There is limited data about antibacterial use in aquaculture
- Also, there is lack adequate knowledge of the pharmacokinetics (PK) and pharmacodynamics (PD) of antibacterial drugs in aquaculture
- Anti-bacterials have been used mainly for therapeutic and prophylactic purposes, while their use as growth promoters is generally rare

- Organisms responsible for disease in aquatic species include:
  1- Bacteria
  2- Fungi
  3- Nematodes
  4- Cestodes
  5- Trematodes
  6- Parasitic protozoa

- Some can cause:
  - ♣ Death
  - ♣ While others may stress the affected fish to the point that it becomes more susceptible to additional diseases

METHODS FOR THE APPLICATION OF ANTIBACTERIAL DRUGS TO FISH

I- Water medication (water-borne route) (baths and dips)

- Is the most common method for administering drugs to fish
- Is necessary if the fish refuse to eat

- Its advantages:
  1- Relatively non-stressful (avoid stressing the fish by handling)
  2- Easy to administer

- Its disadvantages:
  1- More anti-bacterials are required when compared with oral (feed) treatments or injections
  2- Accurate calculation of the volume of water in the tank, pond or cage is also required

- Drugs are added to water for 2 purposes:
  1- The drug will be absorbed by the fish
  2- To kill the free- living and transmissible stages of parasites

- Its types:

  a- Dipping (dips): immersing fish in concentrated medication
  b- Bathing (baths): as dipping but less concentrated & for longer time

  ♣ With these methods, the fish are exposed to solutions/suspensions of the drug for a pre-determined period:

    - For a few seconds (a "dip")
    - For many minutes to several hours (a "bath")

  ♣ Advantages of dipping:

    - The exact dose of drug can be calculated
    - The duration of exposure can be timed perfectly
    - Also, only those fish which are showing symptoms can be treated, leaving the healthier stock

  ♣ Disadvantages of dipping:

    - Only treat the symptoms but not the cause of the problem (bacteria, fungi or parasite) which is still present in the environment of fish **i.e.**
    - The pond as a whole may still harbor infective agents

- ♣ Disadvantages of dips and baths:
    - Mainly used for surface-dwelling pathogens, including parasites, bacteria and water molds **i.e.** for only pathogens on skin and gill
    - Certain species, such as scale-less fish are often especially sensitive to water-borne treatments

- If both short-term (dip) and long-term (bath) exposures are feasible (suitable or can used) and effective, it is preferable to use a short-duration drug exposure which:

    - ♣ Its advantages:
        - Reduced expense
        - Less environmental contamination
    - ♣ Its disadvantages:
        - In most cases less than 5 % of the administered dose will be absorbed by the fish and in this case,
        - The technique is wasteful, and
        - Expensive (at least 20 times the dose required by the fish must be provided)
        - Environmentally un-desirable

- Anti-bacterials which are absorbed from the water include:
    - Dihydro-streptomycin
    - Kanamycin
    - Oxytetracycline
    - Erythromycin
    - Enrofloxacin
    - Flumequine
    - Oxolinic acid
    - Sulphadimethoxine
    - Sulphadimidine
    - Sulphanilamide
    - Sulphapyridine
    - Trimethoprim
    - Chloramines

- Anti-bacterials that are absorbed poorly or not at all include:
    - Chloramphenicol
    - Gentamicin

II- Oral medications (Feeding – Using medicated feed)

- Many of the bacterial diseases of fish can be successfully treated with medicated feeds, and it is usually the preferred method of treatment
- Care must be taken because some of the causes of disease – such as stress – can lead to treatment failures
- Diseased fish may not eat, and with-holding food for 12-24 hours may increase the acceptance of a medicated feed
- The incorporation of an antibacterial in the feed is usually via a powdered premix in conjunction with a binder, such as gelatin or vegetable oil

- The dosage rates used in medicated feeds will vary according to:

  1- The antibacterial used and the level of active ingredient
  2- The fish body weight
  3- The daily feeding rate
  4- The consideration of whether the fish are marine or fresh water species

  ♣ Problems of treatment of marine species:

    - Anti-bacterials are less effective in seawater,
    - Reduced bioavailability
    - **Ex.** tetracycline (TTC) has a low bioavailability in fish (< 10 %) due to binding with sea-water-borne divalent cations such as Mg_2^+ and Ca_2^+
    - Salt-water fish will drink and, therefore, drugs may bind cations in the water in their intestinal tracts, affecting bioavailability
    - The non-bioavailable TTCs contaminate the environment

- Examples of reduced bioavailability for some aquaculture drugs in salmon held seawater:

III- Injection

- More effective treatment for bacterial infections than medicated feed
- Is the best way of being sure of the given dose
- Only for valuable individual fish, such as brood stock & not for fish in large-scale production
- An individual fish will also need to be anaesthetized before treatment
- Typical injection sites include:

1- Intra-peritoneal (IP) route

- The most common, widely and effective used route
- Fish should be fasted for 24 hours prior to injection
- Improper injection can lead to peritoneal adhesion, ovulation problems, mortality from injection, ↓ efficacy, side effects (local reactions), ↓ carcass quality and therapy failure
- The actual IP injection is performed by injecting in the abdomen at a 45 degree angle between the caudal fins and the anal vent

2- Intramuscular (IM) route

- Is performed with similar needle angle and direction for IP, but it is in the muscular tissue along and to the side of the dorsal fin
- The needle must be inserted deeply
- Used only for fish more than 13 cm long or more than 15 gm b.wt.
- Only relatively small amounts can be injected (0.05 ml/50 grams of fish)
- Injections should be done slowly
- Its disadvantages: causing damage to carcass quality and abscesses forming

a- Dorsal muscle injection:

Antibacterial	Bioavailability (%)
Oxytetracycline	1
Amoxicillin	2
Sarafloxacin	2
Oxolinic acid	30
Flumequine	45
Sulfadiazine	50
Trimethoprim	96
Florfenicol	97

♣ This injection site offers the opportunity for deep IM injections

- ♣ Slip the needle underneath a scale, aiming towards the nose of the fish and administer the injection
- ♣ Keep some pressure on the injection site with a thumb for a few seconds to ensure better distribution of the antibiotics and to prevent it from being forced out by contracting muscles
- ♣ Topical treatment can be applied to the injection site to prevent bacterial infection
- ♣ There is immediate risk of scale losses, thus
- ♣ Not recommended for valuable fish

b- <u>Caudal muscle injection</u>:

- ♣ This injection site offers the opportunity for injection into the red muscle of the fish that will ensure rapid distribution of the antibiotics through the fish
- ♣ The needle is also slipped underneath a scale
- ♣ The procedure is similar to the injection into the dorsal muscle
- ♣ There is immediate risk of scale losses, thus
- ♣ Not recommended for valuable fish

c- <u>Base of the dorsal fin injection:</u>

- ♣ The injection site is located at the rear of the dorsal fin, just behind the last fin ray
- ♣ There are no scales at this site and offers an injection site without the immediate risk of scale losses
- ♣ Because this is also an IM injection, apply a little pressure to the injection site when the needle is withdrawn

d- <u>Pectoral muscle injection:</u>

- ♣ Is the best injection site for an IM injection, mainly because there are no scales
- ♣ There are no s cales at this site and offers an injection site without the immediate risk of scale losses
- ♣ With some medications, the muscle tissue of the fish may harden, rendering the fin immobile, especially in smaller fish
- ♣ Topical treatment can also be applied to the injection site to prevent bacterial infection
- ♣ The injection site is located at the rear of the dorsal fin, just behind the last fin ray

3- Intravenous (IV) route

- Some antibiotics are developed for injection directly into the blood-stream, because it loses it's effectiveness quickly
- This can be achieved through an IV injection to the base of the caudal fin
- The main problem that one experience with this specific injection is the ability to penetrate the vein that runs through the center of the fish
- The best way to determine when the needle is placed correctly is to turn the fish upside down and then to insert the needle at the base of the caudal fin
- If you draw the plunger back a little, blood should be entering the syringe

Disadvantages of fish injection:

- Stressing the fish by handling
- The need to bring the fish to the clinic for every injection, because the owner is usually unable to perform the treatment

The volume required for the injection of anti-bacterial is based on:

1- The weight of fish to be treated
2- The recommended dosage for the anti-bacterial being used
3- And its supplied concentration

- This is usually expressed by a formula:

$$\text{Volume of antibacterial required} = \frac{\text{Recommended dosage (mg/kg)} \times \text{Weight of fish (kg)}}{\text{Supplied solution concentration (mg/ml)}}$$

IV- Topical application

- Rare & only for more valuable individual fish, such as brood stock
- Anesthesia is an essential preliminary procedure
- Antibacterial ointments are the most commonly used as in cases of fish surgeries (applied to the sutures and incision site)
- Also a cotton swab can dipped in a drug solution and then used to gently touch the lesion

V- Water treatment

- Disinfection can reduce the risk of disease transmission within

aquaculture facilities, and from facilities to the environment, by deactivating or destroying pathogens with disinfecting agents

- Disinfection can be done routinely, but also in response to the outbreak of specific diseases
- In this procedure the drug is applied to all the water in the aquarium

DRUG DOSAGE IN FISH

- If one is unsure about the dose to use, it is usually best to start with the lower recommended dose
- If the disease does not respond adequately, repeat the treatment with a higher dose
- For oral medications, dosage varies with feed intake
- Fish that are eating less need a higher percentage of the drug in their diet.
- Some drugs are unpalatable at high doses (**Ex.** many anti-bacterials)

- Drug dosage regimens also are host-dependent
- Fish species reared in warm water may absorb, metabolize and excrete drugs at a different rate (often faster) than those in cold water

- The salinity of water also affects drug kinetics
- Fish kept in saltwater drink the water while freshwater fish do not. Thus, anti-bacterials in the GIT of saltwater fish may bind cations, which can reduce their efficacy such as the tetracyclines

- Successful therapy often depends on maintaining adequate blood levels over a course of seven to ten days
- Temperature is very important factor that affect dose & treatment intervals
- PK and PD data are very important for the design of therapeutic regimens

- <u>The following table show some drug dosages and half-lives</u>:
  - ♣ It is important to realize that the dosages listed in this table may not have been shown to be safe or effective in all fish species and no generalizations are possible

Drug	Species	$t_{1/2}$ (h)	Dosage	Route	C°
Amoxicillin	Atlantic salmon	120	12.5 mg/kg single dose	IM	13
	Atlantic salmon	14-72	40-80 mg/kg single dose	IV-Oral	16-22
Oxytetracycline	Atlantic salmon, carp, eel	43-268	10-100 mg/kg up to 10 days	Oral	7-27
	Salmon	428-578	10-100 mg/kg single dose	Oral	6-11
Florfenicol	Atlantic salmon	12-30	10 mg/kg single dose	IV-Oral	10-11
	Cod	39-43	10 mg/kg single dose	IV-Oral	8

- The elimination half-life of antibacterial drugs ↑ significantly as the temperature ↓ (follow the table)

DRUG METABOLISM IN FISH

- Liver is the primary organ for the detoxification of drugs in fish
- Metabolism of drugs are similar in fish and mammals
- The metabolism of aquaculture anti-bacterials by the cytochrome P_{450} system could affect their activation, tissue distribution and elimination rates, and determine the persistence of residues as well as the length of the withdrawal period before the fish can be used for human consumption
- The elimination rate of anti-bacterials from fish tissues varies greatly with the temperature
- The temperature dependency of drug PK is an important consideration for drug residues
- The elimination half-life of antibacterial drugs ↑ significantly as the temperature ↓
- Ideally, the drug dose should be adjusted according to the water temperature

FAILURE OF ANTIBACTERIAL THERAPY

- Treatment failure has many causes:

1- The selected antibacterial may be inappropriate because of misdiagnosis
2- Poor drug diffusion at the site of the infection
3- Inactivity of a given drug at the site of infection
4- Failure to identify the causative agent including in-accurate results

of laboratory tests
5- Resistance of pathogens
6- Intra-cellular location of bacteria
7- Errors in sampling
8- Inadequate dosage
9- Use of drugs with low bioavailability

- Patient factors:

1- Presence of foreign bodies
2- Neoplasia
3- Impairment of host defenses

PROBLEMS ASSOCIATED WITH ANTIBACTERIAL USE IN AQUACULTURE

I- Toxicity to the host

- Host toxicity is the most important factor limiting drug use
- Agents, such as beta-lactams, are generally considered to be safe, but others, such as the aminoglycosides, are toxic

- Antibacterial agents can cause damaging effects to the host, including:

1- Direct host toxicity
2- Adverse interactions with other drugs
3- Interference with the protective effect of normal host microflora or the disturbance of the metabolic function of microbial flora in the digestive tract of herbivores
4- Antibacterial resistance
5- Tissue necrosis at injection sites
6- Drug residues in fish meat and fish products that are intended for human consumption
7- Impairment of the host's immune or defense mechanisms
8- Damage to foetal or neonatal tissues

II- Resistance of aquatic bacteria

- Means: resistance of fish pathogenic bacteria to anti-bacterials
- Where, the bacteria are able to survive after exposure to one or more anti-bacterial
- The bacteria resistant to multiple anti-bacterial are considered multi-drug resistant (MDR)
- In general, aquatic bacteria are not different from other bacteria in human and veterinary medicine in their responses to antibacterial agents
- The fact that some of the bacteria that cause infections in fish belong to

the same genera as the bacteria causing infections in humans is likely to increase the probability of the spread of antibacterial resistance from aquaculture to humans

- Causes and mechanism of resistance:

A- Acquired resistance:

1- Mis-diagnosis which lead to selection of un-suitable anti-microbial
2- In-accurate identification of the causative organism
3- Mis-use (sub-therapeutic or in-sufficient dose) of anti-bacterials
4- Over-use of antimicrobial
5- Incorrect routes of application
6- Incorrect dosing frequencies
7- Administering of anti-bacterials for an in-sufficient time period
8- Use of anti-microbials in feed as feed additives

B- Chromosomal resistance:

1- Production of enzymes by certain bacteria by which they can destroy or caused failure of the activity of anti-microbial agent:

♣ Example: Staph. aureus, E. Coli and Pseudomonas aeruginosa able to produce beta-lactamases (penicillinases) enzymes, these enzymes causes breakdown of beta-lactam ring and thus the PCN molecule become inactive
♣ Example: Certain types of micro-organisms produce chloramphenicol acetyl transferase "CAT" (acetylase) enzyme which destroy or in-activate the drug

2- In-ability of anti-bacterial drug to penetrate the cell wall of bacteria (as due to intracellular location of the micro-organism):

♣ Example: The resistance produced by many G-ve bacteria to the PCN

3- In-ability of anti-bacterial drug to reach its target of action:

♣ Example: Some bacteria produce enzymes (as phospho-transferases "phosphorylation", acetyl-transferases

"acetylation") which prevent the binding of AMGS to their receptor sites on the bacterial 30S ribosomal subunits

4- Production of resistant enzymes by the bacteria to the action of antibacterial drug:

- ♣ Example: Synthesis of resistant dihydro-petroate synthetase enzyme to the activity of sulfonamide agents
- ♣ Example: Synthesis of resistant di-hydrofolate reductase enzyme to TMP

C- Cross resistance:

1- Among AMGS
2- Among TTCS
3- Among polymyxins
4- Among lincosamides (Lincomycin & Clindamycin) & with macrolides
5- Among macrolides (erythromycin, tylosin, tulathromycin)
6- Between erythromycin and lincosamides

- Examples of resistance mechanisms for some antibacterials:

Antibacterial agent	Resistance mechanism
Chloramphenicol	Acetylation in *Enterobacteriaceae*
β-lactams	Degradation by β-lactamases enzymes in *Enterobacteriaceae, Staphylococcus aureus*
Aminoglycosides	Phosphorylation and acetylation of AMGs in Gram–ve and +ve bacteria
Streptomycin	Modification of ribosomal proteins in *Mycobacterium spp.*
Macrolides & lincosamides	Methylation of ribosomal RNA in Gram+ve organisms
Fluoroquinolones	Low affinity DNA topoisomerases to quinolones
Sulphonamides	Resistant dihydro-pteroate synthitase in Gram -ve bacteria
Trimethoprim	Resistant dihydro-folate reductase

III- Aquatic food residues

- The heavy prophylactic and therapeutic use of anti-bacterials in aquaculture environments and with fish food increases the incidence for the presence of residual anti-bacterials in fish meat and fish products

- Withdrawal times are recommended, especially for anti-bacterials
- Also, the accurate and sensitive determination of antibacterial residues is recommended
- In order to protect human health, the maximum residue limits (MRLs) were established for antibacterial residues in animal products entering the human food chain
- Research projects should be promoted on pharmacology and the PK of anti-bacterials in aquatic species in order to provide a more exact approach to establishing MRLs' values

- The antibacterial compounds and their maximum residue limits (MRLs)

Antibacterial	Species	Tissue	Maximum residue limits (MRL)
Amoxicillin	All food producing species (FPS)	Muscle	50 pg/kg
Ampicillin	All FPS	Muscle	50 pg/kg
Benzylpenicillin	All FPS	Muscle	50 pg/kg
Chlortetracycline	All FPS	Muscle	100 pg/kg
Cloxacillin	All FPS	Muscle	300 pg/kg
Colistine	All FPS	Muscle	150 pg/kg
Danofloxacin	All FPS	Muscle	100 pg/kg
Dicloxacillin	All FPS	Muscle	300 pg/kg
Difloxacin	All FPS	Muscle	300 pg/kg
Enrofloxacin	All FPS	Muscle	100 pg/kg
Erythromycin	All FPS	Muscle	200 pg/kg
Florfenicol	Fish	Muscle + skin	1000 pg/kg
Flumequine	Fish	Muscle + skin	600 pg/kg
Lincomycin	All FPS	Muscle	100 pg/kg
Neomycin	All FPS	Muscle	500 pg/kg
Oxacillin	All FPS	Muscle	300 pg/kg
Oxolinic acid	Fish	Muscle + skin	100 pg/kg
Oxytetracycline	All FPS	Muscle	100 pg/kg
Paromomycin	All FPS	Muscle	500 pg/kg
Sarafloxacin	Salmonids	Muscle + skin	30 pg/kg
Spectinomycin	All FPS	Muscle	300 pg/kg

Sulphonamides (All)	All FPS	Muscle	100 pg/kg
Tetracycline	All FPS	Muscle	100 pg/kg
Thiamphenicol	All FPS	Muscle	50 pg/kg
Tilmicosine	All FPS	Muscle	50 pg/kg
Trimethoprim	All FPS	Muscle	50 pg/kg
Tylosin	All FPS	Muscle	100 pg/kg

IV- Environmental effects of antibacterial use in aquaculture

- Aquaculture is linked to the surrounding environment
- The surrounding environment in cases of fish disease and treatment is related to two aspects:
  - **a-** The transmission of microbial pathogens to the surrounding populations
  - **b-** And the pollution from the used chemotherapeutics

- The extensive use of veterinary pharmaceuticals represent a higher public health risk, leading to:
  - **a-** Emergence and spread of resistant bacteria
  - **b-** Human, animal and environmental impairments

- Tetracycline has a low bioavailability in fish (< 10%), due to binding with sea-water-borne divalent cations such as Mg_2^+ and Ca_2^+
- The non-bioavailable tetracyclines contaminate the environment
- The residues of oxytetracycline in marine sediments were very stable over a period of months
- The anti-bacterials, disinfectants and heavy metals being released into water, they may exert damage in water communities, leading to antibacterial resistance

- For example: the exposure of eels to pollution during their development induce changes on the biomarkers involved in physiological functions that are determinants for the survival and performance of the eels, namely biotransformation enzymes and anti-oxidative stress defenses, and these alterations may have negative effects on sexual development