ISOMETAMIDIUM.

Originally known as methamidium or trypamidium

Mechanism of Action.

- It inhibits D.N.A. synthesis in a similar manner as diminazene aceturate.
- It modifies the mitochondrial membrane
- It modifies the glycoprotein structure in surface of the endoplasmic reticulum

Chemotherapeutic uses.

- It is effective against .*T.vivax* and congolense.
- It is effective when trypanosomes are resistant to other conventional drugs.
- It has narrow safety margin and rather a narrow spectrum of activity.
- It is used prophylactically to prevent *T. congolense* and *T . brucei* in dogs.
- It is used in animals during long trek through the tsetse infested sore.
- It is used to confer protection against trypanosomal infection in endemic areas at 3-6 months.

Limitations of the Drug.

- It has narrow safety margin
- It is reported that there is relapse after the use of the drug
- There is severe local reaction at site of injection.

Dose

0.5-1mg/kg body wergilds administered deep intramuscularly or 0.25-0.5mg/kg

Quinapyramine Compounds.

Examples are quinapyramine chloride, quinapyramine sulphate, and suramin these compounds **are dimethyl chloride** is absorbed slowly.

In preparation of the drug 3 parts of **dimethlysulphate** and 2 parts of **dimethyl chloride** this is called "**antrycide prosalt**" and this is used for therapy and prophylexis some-times it is given in combination with **suramin** another **quinapyramine** compound.

Spectrum of Activity.

- It is effective against *T.congolense* and *T.vivax* in cattle and other animals.
- It is also effective against *T.brucei* and *T.evansi*

Limitations of the Drugs.

- It is poorly tolerated by horses.
- It cause serious local reactions at the site and should be given in two or more divided doses at 6hours interval using 5% solution and 10% subcutaneously

Mechanism of Action

- It is a trypanostatic in action and therefore the host defence mechanism is very important in overcoming the infection
- It causes a kinetoplastic D.N.A. condensation.
- It causes the loss of ribosomes with possible aggregate formation with large number of lysosomes.

Dosage

- It is given at 4.4mg/kg in heavier animals
- 150-200kg-1g.
- 200-350kg : 1.5g
- over 350kg
- over 350kg weight :2g

Contraindication

- The drug should not be used in young stock because it cause **sweating**, **salivation, polypnoea, tarchycardia** and death might occur

The Use of the Drug in Horses

- It is used prophylactically in horses especially in the breeding season at an interval 90days between injections is satisfactory.
- Transmission during service can be prevented using quinapyramine 18days before service and it is used to prevent Dourines disease.

SURAMIN

Chemistry:- Surmin is a complex water-soluble derive of urea.

- It is complex aromatic organic compounds
- It is hydroscopic powder
- It has lower solubility in water.

Mechanism of Action

- The drug bind avidly to proteins and inhibits many enzymes among them, are those involved in energy metabolism (e.g **glycerophosphate dehydrogenase).** This mechanism is correlated with the trypanocidal activity.
- It also distorts the intracellular membrane in lysosomes

Uses

- It is used prophylactically and curatively
- It is use against *T.evansi* the cause surra in horses, trypanosomosis in cattle and dogs.
- It is potentiated by phenanthridium and quinidine derivatives

Dosages

- Horses 7-10mg/kg bwt

- Camels 8-12mg/kg bwt
- Cattle 12mg/kg bwt

The dose in horse may be repeated three times weekly interval

Limitation of Surmin

- Narrow margin of safety
- It does not cross the blood-brain barrier so it could not be used in chronic or late stage of trypanosomosis.
- Camel trypanosomosis are quite resistant

Toxicity and Adverse Effects

The toxicity is frequent and severe this thus poses as **nephrotoxity**, **hepatotoxicity** damages to the spleen and adrenal gland.

Synergistic Property of Suramin

Suramin would be as a supergistic potentiator of other drugs (e.g suramin /quinapyramine) (homidium suraminate)

ORGANIC ARSENICALS

An example of organic arsenicals is melarsomin, or melarsoprol.

Organic arsenicals are used in treatment of late–stage of human African trypanosomosis

- It is used in haemolymphatic stage of the disease. the drug is effective in late stage of the disease and it can pass to the blood-brain barrier to cause the therapeutic effect, when the trypanosomes are in the cerebro-spinal fluid and in the C.N.S

Limitations of Organic Arsenicals

- It is restricted to I.V. administration by the W.H.O. to avoid reactions
- There is relapse in melarsonyl than melarsorprol.

- Encephalopathy might occur.

Mechanism of Action

- It combines with the enzyme system in trypanosome trypanothione oxidase reductase system.
- Arsenicals acts by interacting with S.H group which is essential for intracellular metabolic process.
- It also act on the glycolytic enzymes

OTHER TRYPANOSOMAL DRUGS

- Antimony and potassium tartrate used I.V at 3.5mg/kg in horse and cattle and 1-3mg/kg for dogs.
- Stibophen.
- Trypan red
- Trypan blue.

ANTIPIROPLASMAL COMPOUNDS

The clinically important proplasms are anaplasmosis, babesiosis, cowdriosis, theileriosis, ehrlichriosis, hepatozoonosis and in avians spirochaetosis

AMICARBALIDE ISETHIONATE

Chemistry:-chemically made of complex urea compounds.

Uses:-

Used in babesiosis and theileriosis namely *B.divergens, B.cabali* and *Theileria pavae*

Route of Administration

1/m and I.V.

Dosage

5-10mg/kg between .

Toxicity:- It might cause local irritation and localized swelling at the site of administration.

Treatment Regimen for Anaplasmosis

In treatment of anaplasmosis tetracycline and Imidocarb are of value in treatment, prophylaxis, and elimination of carrier –state a single 1/m inj of oxytetracychine at 10mg/kg between will produce cure at 5% conc 2-3 daily doses may be necessary

- If long acting 20mg/kg is needed
- To eliminate the carrier-state, oxytetracycline is administered at a daily 1/m or 1/v dose rate of 11mg/kg for 10-14days.
- Oral chlortetracycline is administered at 45-60days or long acting of oxytet is administered twice at 20mg/kg between 1.m.7days apart
- Imidocrab at 3.5mg/kg birth weight, I.M; the dose is repeated 10-14 days.
- To eliminate the carrier-state, tow intramuscular or subcutaneous doses, each at 4mg/kg, 24 hours.

Treatment of Theileriosis

Like anaplasmosis, there is no specific treatment for theileriosis. But treatment with **buparvquone, halfuginone, menoctone, parvaquone** *and* **tetracycline**.

Infection detected at early stage could be treated using short acting at a dose of 15mg/kg I.M. for 5 consecutive days. The long acting oxytetracycline is administered once at 20mg/kg I.M.

IMIDOCARB (Imidocarbdipropionate)

Physical properties

- It has a white coloured appearance
- It has a melting point greater than 200^{o}C

Chemistry

Imidocarb is a carbanilide dimidines

Uses:

- It is efficacious against babesiosis in dogs.
- Anaplasmosis (in cattle)
- Ehrlichiosis in dogs.
- It could be used prophylactically and therapeutically.

Pharmacokinetics:

After I.V. injection in sheep the drug would reach its peak in the plasma level of $10.8mg/ml^{-1}$, this would drop to $1.9mg/ml^{-1}$ in an hour.

It can be detected in the blood for 4 weeks.

The drug is detected in urine and faeces in an unchanged form.

Dosage:

Imidocarb is administered either I.V., I/M or S/c.

Babesiosis Therapy

Cattle - 1.2mg/kg birth weight

Horse - 2.4m,g/kg birth weight.

Dogs - 6mg/kg birth weight

Anaplasmosis Therapy

Cattle – 3mg/kg birth weight

Safety and Toxicity

It has a very high safety margin in rats and dogs.

It has low safety margin in cattle.

Withdrawal period.

Withdrawal period of the drug is 28 days.

Sometimes 90 days withdrawal period might be required after last treatment.

QUINURONIUM SULPHATE

Quinuronium sulphate is used against *Babesia cabali, B. bouis, B. ouis, B. molasi*. The drug is used in febrile stages in 24 - 48hrs a second treatment might be necessary. The course of treatment might be repeated for 2 weeks but preferably for 3 months.

Premunity and Quinoronium

The drug should not be used for a long duration. This might cause animal susceptibility to piroplasms. Therefore it is preferred to inoculate the animal with virulent strain of the parasite, but at a dose lower than the dose that will cause the disease.

Dosages:

0.3-0.5mg/kg birth weight for cattle, sheep, pigs and in rats. 0.5mg/kg birth weight for dogs, 0.25mg/kg birth weight. The drug should be diluted by 120 times i.e. 0.5%, but officially the drug is concentrated at 5%.

Toxicity

- Tremor
- Salivation
- Urination
- Defecation

- Shock might occur due to fall of the blood pressure.

Other Anti-proplasmosis drugs are:

- *Trypan Blue*
- *Diaminazene*
- *Trypan red*

ANTIHISTOMONIASIS

- Aminonitrothiazole
- Nithiazide

TREATMENT OF GIARDIASIS

- The main drugs used for treatment of giardiasis are follows: Metronidazole, dimetridazole, pronidazole, tinidazole, nimorazole these are know as 5 –nitroimidazoles

Spectrum of Activity

- It possesses a broad spectrum of activity.
- It is effective against trichomonads, **amoebae** and **giardia** and **bacteria** (anaerobic *cocci* and *bacilli*).

Mechanism of Action

It disrupts D.N.A. synthesis in protozoans and bacteria.

Pharmacokinetics

The oral bioavailability of metronidazole varies from 50-100%. If given with food absorption is enhanced in dogs.

- The absorption is due to increased of bile secretion that helps to dissolve the drug.
- Peak blood levels reaches in 1hour of dosing
- Distribution is wide and rapid due to lipid solubility

- The drug is metabolized by **glucuronide** and **several oxidation products** that may darken the urine.
- Elimination **half –life is 3-5hours** in dogs and horses.
- Excretion takes place in 24hour, the drugs metabolite and unchanged from of the drug is excreted in faces and urine.

Dose

- Canine giardiasis 25mg/kg po.IV or SC bid
- Equine trichomoniasis 20mg/kg by slow infusion
- Bovine trichomoniasis 75mg/kg IV bid
- Topical application 5% ointment plus urethral douche; to irrigate wound

The course of treatment is 5-7 days. When treating birds or rodents metronidazole is added in drinking water in amoebiasis.

Adverse Effect of Metronidazole

- Nausea, vomiting, abdominal cramp
- High doses in dogs may produce neurological disturbances characterized by tremor, weakness, muscle spasm, ataxia and convulsion
- Experiments in rats show that it is mutagenic if used for a prolonged time.

Other drugs used in gastrointestinal protozoan infections

Examples:

1) *Toxoplasma gondii* is treated using

- **Sulfadiazine** (15-20mg/kg).
- **Atavaguine** and **spiramycin** are used in difficult cases of toxoplasmosis
- **Clindamycin** at 10-40mg/kg used in dogs 20-50mg/kg but in cats

2) **Amoebiasis :-** caused by *entamoeba hystolitica* is not common in animals but *E. invadei* in reptiles is treated using metronidizole at 10-25mg/kg bid orally for /52 or one week **furazolidine** 2-4mg/kg orally t/d
3) **Cryptosporidiosis:-** In neonates eg calves, kids, lambs piglets, it is usually caused by *Cryptosporidium paroum* **paromomycin sulphate**

ANTICOCCIDIAL DRUGS.

The major drugs used are classified as

- Sulphonamides
- Quinazolines
- Quinolones
- Symmetrical triazinones
- Thiamine antagonists

SULPHONAMIDES

The sulphonamides used are:

- Sulphadimethoxine
- Sulphaquinoxaline
- Sulphaclozine sulphaclozine

Usually sodium salt of sulphadimethoxine (0.1%) or sulphaquinoxaline (0.02 per cent) is given in drinking water. Medication may continue for 3.5days intermittently

Precaution to avoid toxicity “the intermittent method” is preferred this consists two medical periods, each of **3days-2days apart another 3days**, when normal food and drinking water is provided.

Sulphonamide preparations incorporating diaminopyrimidine potentiators are available for use in small animals (eg. Sulphadimidine with *trimethoprim or ormethoprim, sulphadiazine* with trimethoprim.

Limitations of Sulphonamides in Treatment of Coccidiosis

- None of the sulphonamides are broad spectrum for coccidiosis.
- They are previously not active against early asexual coccidian parasites.

Dosage

- In turkeys, achieved when 125ppm daily in food or water for 8weeks. Also treatment using 500ppm for 7days preferably in water.

In Rabbits

Prophylactic treatment is 250ppm daily in feeds as premix for 7days or treatment 1000ppm in water for 7days preferably in water

In Cattle

Prevention is achieved using 13mg/kg

Withdrawal Time in Days

- 28days before point of lay
- 75days before slaughter of animals.

Quinazolines

Example halofuquinone derived from febrifugine an extract of plant

- It is potent drug.
- It can be used in avian species
- Usually a steep dose – response curve is achieved when using the drug.

Use:

Usually used in turkey and chicken

Dosage: chicken 3ppm in feed

Turkey the drug is same as chicken and should be used for 12 weeks.

QUINOLONES.

Examples:

- Decoquinate
- Methylbezoquate
- Nequinate

Quinolones: Their activity is essentially coccidiostatic used against invading sporozoites.

- Should be used in early stage or prophylactically the drug would not be effective if delayed.

Mechanism of action.

The quinolones selectively inhibit the electron transport chain in the *emeria* parasite.

Use:

Decoquimte could be used in food as premix or in water as powder for prevention of coccidiosis in broiler chickens.

Dosage:

Broilers: 20-40 ppm in food

Ewes: 100ppm for 28days

Cattle: 500ppm in feed

SYMMETRICAL TRIAZINONES

Example :- Toltrazuril

This is a drug produced for its coccidiostatic property used against sporozoites

- It is also potent *schizogony* and *gametogony*
- In the use of the drug the drug is usually interpreted for 2-3 days of medication.

Spectrum of Activity

It is effective against *E. tenella*

It is used in turkeys, rabbits and chicken

Dosages

- Broilers 25ppm in drinking water
- Rabbit 10-15ppm

Contraindication

Poultry formation are different from rabbits except otherwise

THIAMINE ANTAGONIST

e.g Amprolium

History :- First used in the 60's and was the leading drug until mid- 70s

Spectrum of Activity

- It is used in confirmed *E.acervulina* and *E. tenella*
- When mixed with *ethopabate* it broadens its spectrum against *E.brunetti* and *E. Maxima*
- Some times used with sulphaquinoxaline to potential its activity
- It is used in chickens, rabbits and ruminants.

Dosage

- 125- 150ppm in feed continuously
- *5mg/kg* in water in calves for 21 days for treatment and used for 5 days for prophylaxis

Dosages with other drugs

125ppm Amprolium + 8ppm ethopabate or 100ppm amprolium + 5ppm ethopabate + 60ppm sulphaquinoxaline.

Contraindication

The drug “Amprolium” should not be used for a long time without using vitamin supplement, because it might predispose the flock to thiamine deficiency.

OTHER ANTICOCCIDIALS

Pyridines

Examples: clopidol

Clopidol does not allow natural immunity to develop

It is used in turkeys, rabbits and chicken.

Dosage

In chicken 125ppm in feed

In rabbits 20ppm in feed

Contraindications

It should not be used with other drugs.

IONOPHORES(polyether antibiotics)

Examples : used in coccidials are

- Monensin
- Lasalocid

Monensin is produced from *strep cinnamonensis* Lasalocid produced from *strep lasaliensis*

Dosage of Monensin

- Chicken layer at 100 – 120ppm

- Turkey 100ppm
- Cattle 16.3 – 33ppm in feed
- Sheep 11-33ppm in feed

Mechanism of Action

Polyethers of monesin and lasalocid the polyethers interfere with transport of ions through membranes causing influx of positively charged ion cations this distorts the osmotic balance of the parasite so it dies.

Other anticoccidials are nitrobenzamides: eg *dinitolmide, alkomid nitromide*

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