Cetrimide

Silver Compounds

In one form or another, silver and its compounds have long been used as antimicrobial agents. The most important silver compound currently in use is silver sulfadiazine (AgSD), although silver metal, silver acetate, silver nitrate, and silver protein, all of which have antimicrobial properties, are also in use. In recent years, silver compounds have been used to prevent the infection of burns and some eye infections and to destroy warts.

Silver nitrate: The mechanism of the antimicrobial action of silver ions is closely related to their interaction with thiol (sulfydryl, ─SH) groups , although other target sites remain a possibility. A 1% solution of silver nitrate is applied to the eyes of newborn infants to prevent opthalmia neonatorum caused by *Gonococcus* but this practice has been replaced by penicillin ointment which is more effective and less hazardous, Ag nitrate caustic pencils are used to cauterize small wounds like skin ulcers and for the destruction of horn buds from the scalp of calves.

Other mercurial organic compounds that have been used for skin cleansing are thiomersal, nitromersal and phenylmercuric nitrate.

Dyes

- These include gentian violet, acriflavin and brilliant green. Antibacterial activity was first discovered in 1913. Now used on wounds and sores.

Biguanides

Chlorhexidine: Chlorhexidine is probably the most widely used biocide in antiseptic products, in particular in handwashing and oral products but also as a disinfectant and preservative. This is due in particular to its broad-spectrum efficacy, substantivity for the skin, and low irritation. Of note, irritability has been described and in many cases may be product specific. Despite the advantages of chlorhexidine, its activity is pH dependent and is greatly reduced in the presence of organic matter. Disrupts cell wall by reacting with well charged groups on protein, lipopolysaccharides and phospholipids. Active against most G+ve and some G-ve bacteria, but not against spores. One of the most commonly used surgical and dental antiseptic. It is incorporated in shampoos, ointments, skin and wound cleansers, surgical scrubs etc. It can be effectively combined with other disinfectants.

Alexidine: Alexidine differs chemically from chlorhexidine in possessing ethylhexyl end groups. Alexidine is more rapidly bactericidal and produces a significantly faster alteration in bactericidal permeability.

Furan derivatives

Nitrofurazone is used as a 0.2% powder or ointment for the treatment of superficial bacterial infections of wounds, burns, cutaneous ulcers and eczema.

GROWTH PROMOTERS/GROWTH PERMITANTS

(Natural/Non-antibiotic Growth Promoters (NGPs) or Antibiotic Growth Promoters (AGPs).

As the name implies, this refers to hormones (natural or synthetic) or antimicrobial compounds which help to improve animal performance. They act by improving growth rate and feed conversion efficiency in livestock on an optimal plane of nutrition.

Antibiotic Growth Promoters (AGPs): The antimicrobial compounds act by changing the population of microbes in the GIT of healthy animals thereby preventing disease and maintaining health in animals in an environment likely to lead to decreased performance due to increased incidence of disease. They are given at low dose rate in contrast to the dose required for therapeutic effect. They should not be used unless they are officially approved and local regulations are followed. Their use has been banned in most countries.

Antimicrobial feed additives

i. Non-ionophore antibiotic e.g avoparcin and flavophospholipol

ii. lonophore antibiotic e.g monesin and lasalocid

iii. Gut-active growth promotants e.g enzymes (amylase, lipase) and probiotics (selected strains of lactobacilli and streptococci). Probiotics are live microorganisms or viable spores which support the development of a beneficial gut microflora. Probiotic bacteria (e.g. from the genera *Lactobacillus, Bifidobacterium, Enterococcus*) counteract undesired microorganisms such as *Salmonella* or *E. coli* by blocking receptors on the gut wall, production of antimicrobial substances or activation of the immune system.

Natural Growth Promoters (NGPs) or Non-antibiotic Growth Promoters: They are commonly regarded as favorable alternatives to Antibiotic Growth Promoters (AGPs) in livestock production.

Categories of NGPs:

NGPs include predominantly acidifiers e.g organic acids, probiotics, prebiotics, synbiotics, phytogenics, feed enzymes and immune stimulants. Since the use of AGPs has been banned, an ongoing search for alternatives has created a large variety of NGPs for pigs, poultry, ruminants and aquatic species.

General benefits of NGPs:

The main advantage of NGPs over AGPs is that they do not bear any risk regarding bacterial resistance or undesired residues in animal products such as meat, milk or eggs. Addition of NGPs to feeds of farm animals may have a number of beneficial effects, including:

- rapid development of a healthy gut microflora
- stabilization of digestion
- increased growth performance
- stimulation and rapid maturation of the immune system
- reduced incidence of diarrhea
- improved feed efficiency
- lower mortality rates
- higher profitability

Steroid Hormones

i. Endogenous steroids: Produced naturally in the gonads e.g estradiol, progesterone and testosterone.

- Estradiol: increase nitrogen retention, growth rate by 10-20% in steers, lean meat content by 1-3% and feed efficiency by 5-8%.
- Testosterone: Normally used as a formulation with estradiol.
- Progesterone: Its major use is to slow down the release of estradiol from compressed pellet implants.

ii. Synthetic steroids: They are generally more potent and have less androgenicity and thus less adverse effects on behaviour. They are androgens e.g trembolone acetate (TBA) or progestogens e.g melengestrol acetate (MGA).

Nonsteroidal Hormones

Two major compounds fall in this class namely:

i. Stilbene estrogen e.g diethylstilbesterol (DES) and hexestrol. Currently banned in most countries because they are genotoxic

ii. Zearelenone (Zeranol)

Growth Hormone

Also increases growth rate, feed conversion efficiency and lean meat in the carcass.

Beta Adenoceptor Agonist

Its major use is to induce change in body composition leading to decreased fat and increased lean meat content.

Acidifiers

Acidifiers, such as organic acids or their salts, are used to prevent microbial degradation of raw materials or finished feeds, especially under poor storage conditions (e.g. high moisture content, high levels of contamination with molds). Moreover, acidifiers may improve growth performance through establishment of low gastrointestinal pH conditions which support endogenous digestive enzymes and reduce undesired gut microorganisms. Many dietary acidifiers are based on propionic acid, formic acid, lactic acid and others, either as single

components or in combination. Some acidifiers also contain inorganic acids (e.g. phosphoric acid).

Prebiotics

Prebiotics are carbohydrates which are indigestible for the host animal. On the other hand, they are selectively fermented by beneficial gut bacteria and, therefore, support a healthy gut microflora.

Synbiotics

Combined administration of probiotics and prebiotics, referred to as synbiotics, is supposed to cause synergistic effects in terms of gut health and performance.

Phytogenics

Phytogenics are derived from herbs, spices or aromatic plants and have shown antimicrobial, antifungal, antiviral, antioxidant or sedative properties. They are known for their appetizing effects, since they increase the palatability of the feed and stimulate endogenous digestive enzymes. Moreover, phytogenics have a pronounced impact on the gut microflora.

Feed enzymes

Animal feeds contain varying levels of indigestible nutrients and undesired components such as fiber, phytate or proteins with antigenic effects. Different feed enzymes such as, carbohydrases, phytases or proteases, can be included in feeds to improve the utilization of energy and nutrients or to degrade several undesired components. Moreover, some enzymes (e.g. amylases, lipases) can be added to the feed of young animals in order to support the endogenous enzyme secretions

Immune stimulants

Different feed additives may function as stimulator or modulator of immunity processes. Specific cell wall fragments from bacteria or yeasts or sea algae may induce activation of immune cells (e.g. macrophages, lymphocytes).

ANTHELMINTIC DRUGS

Overview

Infestation with parasitic worms (or helminthes) is the most important cause of chronic ill health in domestic animals in the tropics. The parasitic helminthes of animals are broadly classified into nematodes (roundworms, hookworms, whipworms, pinworms, schistosomes); annelids (leeches), and acanthocephales (thorny-headed worms). In the animal body, gastrointestinal tract is the abode of many helminthes, but some also live in tissues or their larvae migrate into tissues.

Anthelmintics are drugs that reduce parasite burdens in the animal to a tolerable level; they kill the parasites (*vermicide*), inhibit their growth or paralyze them (*vermifuge*). The also reduce the build-up of infective worm larva on the pasture, or eggs in the environment.

Modes of action- anthelmintics drug regimens are at alteration of metabolic processes that are present in the parasite, but are either absent from or have different characteristics than those of the host. The imidazothiazole athelmintics (e.g. **levamisole**); the terahydroprimidines (e.g. **pyrantel**); the quatemary ammonium salts (e.g.**thenium cloyslate)**, and the pyrimidines (e.g. **methyridine**) act as depolarizing neuromuscular blocking agents, causing persistent activation of the parasite's nicotinic receptors, muscle contraction and spastic paralysis. The organophosphorus compounds (e.g. **dichlorvos**) are cholinesterase antagonists causing excessive build-up of acetylcholine leading to spastic paralysis. They have anthelminitic and insecticidal action. **Piperazine** is a γ-aminobutyric acid (GABA) agonist at receptors on nematode muscle. It blocks acetylcholine at the myoneural junction in the parasites, causing flaccid paralysis: unable to maintain their position in the host, live worm are expelled by normal peristalsis. **Diethylcarbamazine,** a piperazine derivate, blocks host endothelial cells and microfilaria enzymes, cyclooxygenase and synthetase involved in the synthetase of prostaglandins; it enhances nonspecific innate immune system. The avermectins (e.g, **ivermectin)** target the parasites GABA receptors. They intensify GABA-mediated transmission of signals in peripheral nerves by increasing the opening of glutamate-gated chloride channels. Chloride influx is enhanced and hyper-polarisation occurs, resulting in paralysis of nematodes and arthropods. **Praziquantel** causes disruption of the parasite integument and/or muscle membranes by increasing the permeability of cell membrane to calcium, causing contraction and paralysis of the

worm. The benzimidazoles (e.g. **thiabendazole**) and the pro-benzimidazoles (e.g. **febantel**) bind to and interfere with the synthesis of parasite's microtubules. They also decrease glucose uptake. Affected parasites are expelled with the faeces. Salicylanilides (e.g. **closantel**) and substituted phenols (e.g. **nitroxynil**) are proton ionospheres; they uncouple oxidative phosphorylation in the tegmen and mitochondria, inhibiting anaerobic metabolism and glucose uptake. The aromatic amide, **diamphenethide** is a prodrug; it is deactylated to active monoamine and diamine forms. It affects the parasite glycolytic pathway, producing an elevation of malate concentrations, an intermediary breakdown product of glucose metabolism. **Clorsulon,** a benzene disulphonade, inhibits the enzymes, phosphoglycerate kinase and mutase in *fasciola,* thereby inhibiting glucose utilization, and acetate and propionate formation.

Benzimidazoles

The benzimidazoles are the largest chemical family of anthelmintics used in domestic animals. They include **albendazole, carbendazole, fenbendazole, flubendazole, mebendazole, oxfendazole, oxibendazole, parbendazole** and **triclabendazole.** The probenzimidazoles (**fabantel, netobimin,** and **thiophanate**) are converted in the body to **fenbendazole, albendazole,** and **lobendazole**, respectively. Some of the benzimidazoles (albendazole, cambendazole, oxfendazole, parbendazole) are teratogenic and, depending on the dose, are contraindicated in early pregnancy, and require withdrawal periods when used in foods animals.

Anthelmintic spectrum. The benzimidazoles are effective against a wide spectrum of nematodes and have a wide safety margin. Most are effective against larval and adult roundworms. Thiabendazole, febantel, fenbendazole oxfendazole, and oxibendazole are also ovicidal, and thiabendazole is fungicidal in vivo. Triclabendazole is effective against both immature and adult flukes, but has no activity against nematodes. Thiabendazole is effective against worms of the *strogyloidea, ascaroidea* and *trichinelloidea*. In cattle, sheep and goats, more than 95 percent activity is exerted against the common gastrointestinal nematodes (*haemonchus, trichostronglyus, cooperia, ostergia, nematodirus, bunostomum, stronglyloides, oesophagostomum* and *chabertia*). It is effective against the strongyles, ascarids, and oxyurids of horses and the gapeworm (syngamus trachea) of poultry. Thiabendazole has its optimum efficacy in pigs against Hyostronglus rubidus, Oessophagostomum dentatum, and strongyloides ransomi.

Pharmacokinetics – because most benzimidazoles are sparingly soluble in water, they are given per os as suspension, paste, or powder, or by intraruminal injection. Gastrointestinal absorption varies, depending on the water solubility of the compound. Thiabendazole is rapidly absorbed from the gut and peak blood concentrations occur in 4-7 hours. It is widely distributed in the blood and quickly metabolized to 5-hydroxythiabendazole, followed by clearance in the urine (with 5 percent in the faeces. As the the glucuronide or sulphate conjugate). The pre-slaughter withdrawal period in cattle is 27 days for albendazole, 8days for fenbendazole, and 7days for oxfendazol. Resistance and cross-resistance develop fairly readily to members of the group.

Therapeutic uses. The anthelmintic activity of benzimidazoles is related to the duration of therapeutic blood concentrations. Does may need to be repeated for 3-5 consecutive days in pigs, dogs, and cats, while single doses are sufficient in ruminants and horses because the rumen or large intestine acts as a drug reservoir.

In ruminants, albendazole and oxfendazole are effective against major gastrointestinal worms (in both the adult and larval stages). In additions, they are effective against lung worms. However, they are ineffective filarial. In horses, fenbendazole, oxfendazole, oxibendazole, mebendazole, being effective against strongyles, intestinal threadworms and ascarids, but not against bots. Fenbendazole is effective against harbronema, and mebendazole against lungworms at dosages of 15-20mg/kg/day for 5 consecutive days. In dogs and cats, fenbendazole, membendazole, oxibendazole, and febantel are effective against ascarids, hookworms, and whipworms. Febantel is the only agent approved for use in cats.

Mebandazole - is used for the treatment of trinchinosis, particularly at the muscular stage of trinchinella spirals.

Dose, thiabendazole

Horses, sheep	44-88mg/kg (depending on parasite)
Cattle	66-110mg/kg (depending on severity)
Pigs	60-80mg/kg
Poultry	0.1% in the diet.

Imidazothiazoles

Tetramisole, butamisole and **levamisole** are broad-spectrum synthetic imidazothiazole derivatives, which are nicotine-like. They are effective against adult and larval nematodes of the gastrointestinal tract, heart, lungs, and kidney. The anthelmintic activity of tetramisole, a

racemic, mixture, resides in the levo-isomer, levamisole. The dose can be reduced using levamisole alone, which also appreciably increases the margin of safety. This is especially low in horses and dogs. Levamisole has an immunomodulating effect. It restores depressed T – lymphocyte function and potentiates the activity of phagocytes. Beneficial effects of its immunostimulant action have been observed in calves, dogs, cats, and human patients with immuno deficiencies, chronic infection, inflammatory disease and some malignancies. Intermittent treatment with one-third of the normal therapeutic dose for 3-day period separated by 3 days without dosing seems to provide the optimum, response.

Butamisole is a derivative of levamisole. It is an injectable preparation used to treat whipworms and hookworms and hookworms in dogs. It has microfilaricidal activity against heartworms; therefore, it may cause anaphylactic reactions when used in microfilaramic animal.

Pharmacokinetics. Levamisole is formulated for oral and subcutaneous injection in ruminants and pigs. It is rapidly absorbed orally or from the injection site. The half-life is about 4 hours after intrasmuscular administration in the cow. The liver and kidney are the main organs involved in the metabolism and excretion of levamisole. The drug is eliminated from the body in 2 days. The preslaughter clearance periods in pigs and cattle are 3days and 7 days, respectively.

Dose

Ruminants, pigs	7.5mg/kg PO (in feed) or SC
Cats	5mg/kg PO

Levamisole – has been combined with triclabendazole with oxyclozanide for treatment of roundworms and flukes in cattle, and sheep. But, co-administration of levamisole and pyrantel, another nicotine-like nematocide, increase toxicity.

Adverse effects. Levamisole is one of the most toxic anthelmintics; signs of toxicity include salivation and muscle tremors.

Tetrahydropyrimidines

Pyrantel, its methyl ester **morantel**, and the **metaoxyphenol** analogue, **oxantel** are effective against adult gut nematodes. They are less effective against immature forms and are not effective for treating hypobiotic larvae or lungworms. A particular attribute of morantel is its formulation. It is marked as sustained-release bolus; this provides continuous release of the drug in the recticulo-rumen for at least 90 days on oral administration. Pyrantel is formulated as a paste, suspension and granules for broad-spectrum control of adult gut nematodes in horses and

dogs. Along with mebendazole, pyrantel is effective in the treatment of infections caused by roundworms, pinworms, and hookworms. Pyrantel has been combined with oxantel for their broad-spectrum anthelmintic activity. Pyrantel has a good safety margin; it is suitable for use in young puppies, and in pregnant and lactating bitches.

Pharmacokinetics- following oral administration, pyrantel tartrate, being water-soluble, is well absorbed from the gastrointestinal tract of dogs and pigs, and poorly absorbed in ruminants. Morantel tertrate is absorbed rapidly from abomasums and small intestine. Peak plasma levels occur 4-6 hours after dosing. The drugs are quickly metabolized and excreted, mostly via the faeces, but also via urine. Preslaughter withdrawal requirements are 1 day for pyrantel tartrate in pigs and 14 days for morantel in cattle.

Dose

Pyrantel emboate

Horse	19-38mg/kg PO
Dog	14.4mg/kg PO

Adverse effects.

Emesis may occur in dogs and pigs.

Organophosphate anthelmintics

Haloxon, coumphos, dichlorvos, crumate and **napthalophos** are widely used organophosphate anthelmintics. Dichlorvos is used in horses, dogs, pigs, and cats, and **trichlorfon** (metriphonate) in horses and dogs. Haloxon is probably the safest organophosphorus anthelmintic for use in ruminants. The concentration required to inhibit cholinesterase activity of the parasite is extremely low; in addition, mammals have cholinesterase that forms unstable complexes with haloxon. It is primary action ruminants is against parasites of the abomasums and small intestine. It is active against Haemonchus, Trichostronglus, Cooperia, and stronglyloides species. Haloxon may be administered orally in bolus, drench, or paste form at a dose of 44m/kg to cattle, and 35-50 mg/kg to sheep and goats. It is rapidly absorbed from the gut, metabolism fairly rapidly, and excreted in the urine.

Dichlorvos and *trichlorfon* are effective against a broad spectrum of other gastrointestinal helminthes particularly effective against ascarids and bots. These include *trichuris, Habronema, Spiruroides, and Ancylostoma,* but are ineffective against migrating larvae, tapeworm or flukes.

Dichlorvos is available as an in-feed formulation for nematode control in pigs and horses at a dose rate of 30-40 mg/kg. *trichlorfon* is formulated as a paste for use in horses.

Adverse effect: In acute toxicity, there is stimulation of cholinergic receptors in salivation, lacrimation, urination, and diarrhea. Organophosphates may induce chronic neurotoxicity causing demyelination. Acute death may result from respiratory paralysis and cardiovascular arrest.

Avermectins

The avermectins are a group of naturally occurring macrolides (macrocyclic lactones) extracted from sytreptomyces avermitilis. **Ivermemectin, abamectin, epinomectin, moxidectin, doramectin, selamectin,** and **milbemycin oxime** are semi-synthentic avermectin derivates. *Ivermectin* is the most widely used. It has a high degree of efficiency at low doses against all major gastrointestinal worms and lungworms, as well as canine heartworm. It is also effective against all ectoparasites. It is used especially to control lice and manage mites. It is effective in visceral larva migrans, warbles in cattle, and is the drug of choice for *Onchocerca volvulus*, the cause of river blindness in humans. **Milbemycin oxime** is isolated from *Streptomyces hygroscopicus*.

Pharmacokinetics- Ivermectin is rapidly absorbed orally. It is widely distributed, but enters the eye slowly and to a limited extent. More than 95 percent of the absorbed dose is metabolism in the liver. The plasma half-life is 3days in cattle, but remains in tissues with long persistency; one dose is usually effective for 2-4 weeks. Excretion of the drug and its metabolites is almost exclusively in the faeces. Preslaughter clearance periods of ivermectin are 18 days in swine and 35 days cattle. The drug should not be administered to lactating diary cattle, but it is safe for use in pregnant animals and breeders.

Dose:

Cattle	200µg/kg SC
Pig	300µg/kg PO
Sheep	50µg/kg SC
Dog	50µg/kg SC
Dog (heartworm prophylaxis)	6µg/kg PO, monthly
Poultry	up to 160ug/kg PO

Adverse effects – Local irritation may occur following subcutaneous administration to swine. High doses may evoke CNS depression as evidences by listlessness, ataxia, mydriasis, recumbency and coma.

Piperazine

Piperazine is available as the hexahydrate (which contains about 44 percent of the base) and as a variety of salts: adipate, citrate, phosphate, tartrate or hydrochloride. It is effective against *ascarids* and nodular worms in all species; however, it use is limited in ruminants, because *ascarids* are not a significant problem in this species. Piperazine salts are well absorbed orally. The drug is partly metabolized in the liver and the remainder (30-40 percent) is excreted unchanged in the urine. Urinary excretion starts as early as 30 minutes after dosing, and is complete within 24 hours.

Dose

Horse, cow	0.2gm/kg; maximum 80 gm; foals 30 gm; yealings 60gm
Sheep, goat	0.4 -0.8 gm/kg
Pig	0.1 gm/kg in each of 3 successive feeds
Dog, cat	80-240 mg/kg PO
Poultry	up to 160 mg/kg PO

Horses are usually given the drug by tube or mixed with bran mash; other animals and poultry receive it in the drinking water, as a drench, or in the feed. It is non-toxic and is often combined with other anthelmintics to enhance its anthelmintic spectrum in the horse. Thiabendazole is combined with piperazine to increase ascaricidal activity. The addition of carbon disulphide enhanced activity against Gasterophilus bots in the equine stomach, while trichlorfon and phenothiazole combined with piperazine enhance elimination of both pinworms and ascarids.

Adverse effects: Piperazine is almost free of pharmacologic action in the host. It is a very safe drug, but large doses may produce vomiting, diarrhea, and ataxia.

Phenothiazine

Phenthiazine**,** the oldest antinematodel drug, was introduced in 1938. it was used extensively in livestock but has been largely replaced by drugs with broader spectra of activity. It is still used, primarily in ruminants, in prophylactic, low level in-feed programmes. Its efficacy is best against haemonchus and Oesophagostomum species in ruminants, small strongyles in horses, and the

caecal worm (*Haterakis gallinarum*) of poultry. It is mixed with piperazine is not recommended for use in pigs, dogs or cats because it is toxic and possesses little effectiveness in these species.

Dose:

Single oral therapeutic doses (in food, as a drench, or by stomach tube, or in tablet form or salt lick):

Horses	10-30 gm at 3 mg/50kg
Cattle	20-60gm at 10gm/kg
Sheep, goats	5-40gm
Poultry	0.25-1 gm

Repeat doses:

Horses	2-5gm
Foals	1-2gm
Cattle	0.5-5gm (0.5gm per 45kg)

Daily prophylactic doses:

Horses	300mg
Sheep	1 part phenthiazine 9 or 10 parts mineral or plain salts.

Adverse effects: Phenthiazine may evoke dullness, weakness, anorexia, oliguria, and signs of haemolysis (aneamia, icterus, haemoglobinuria). It may cause haemolytic anaemia especially in horses by activating the enzyme iysolecithin. This enzyme is normally found in horses blood and has been shown to lyse red blood cells in vitro. Photosensitation due to the sulphoxide metabolite and occurring 2-3 days post-treatment is not uncommon in keratitis and comeal ulceration.