

CHLORAMPHENICOL, MACROLIDES, LINCOSAMIDES AND SULPHONAMIDES

CHLORAMPHENICOL

History:

- First isolated in 1947
- First synthesized in 1949
- It is the first commercially synthesized antibiotic.

Source:

- It was first isolated from *Streptomyces venezuelae*
- Later synthesized artificially.

Chemistry:

- Chemically, it is derived from dichloroacetic acid containing a nitrobenzen moiety.
- It is a neutral stable compound.
- Plamitate salt is its form of salt and it is water insoluble thus, it is administered orally.
- While the *Sodium succinate* salt for parenteral use is water soluble.

Mode of action:

- Chloramphenicol binds with the 50 s ribosomal subunit to inhibit peptide bond formation and protein synthesis in the bacterial or disease causing organism.

Antimicrobial Spectrum

Chloramphenicol is a broad-spectrum bacteriostatic agents active against many gram-positive and gram-negative bacteria, *Rickettsia*, *Mycoplasmas*, and *Chylamydia*. It has an excellent therapeutic activity against *Salmonella*.

Resistance: The resistance bacteria inactivate chloramphenicol by *acetyl-transferase* and other enzymes.

Pharmacokinetics:

- Following oral administration, chloramphenicol is rapidly absorbed especially in monogastrics.
- The peak plasma concentration is attained in dog about 30 minutes after an intramuscular injection.
- The drug becomes widely distributed in the tissues including those of the eye.

- The circulatory chloramphenicol becomes bound to red blood cells and plasma proteins producing similar concentration in cells as in plasma.
- The drug is widely metabolized in the liver by nitro-reduction and glucuronide conjugation. This metabolism is rapid in the horse.
- The drug is eliminated entirely in-active in its metabolites in urine and faeces via the entero-hepatic shunt.

Why chloramphenicol is not administered orally in ruminants for the following reasons:

1. Nitro-reduction takes place in the rumen due to the rumenal flora.
2. The drug would be inactivated or would lose its therapeutic value.

Therapeutic Uses:

- Its use is restricted to life-threatening infections, such as systemic *salmonellosis* and respiratory disease in calves.
- The drug is used in humans in typhoid fever.
- 1% topically or 0.5% solution is used in the treatment of acquired *Dermatophilus* infection.
- Ovine foot rot.
- Mastitis in cattle
- In skin and eye infections.

Adverse Effects:

- The effect of chloramphenicol via its protein synthesis inhibition might be on specific to the cells of bacteria thus, since the mitochondrial ribosomes of mammals or the host is similar to the bacteria, this might predispose to toxicity of bone marrow.
- There is a dose-related anaemia associated with the use of this drug especially in cats, ducks and dogs.
- In man, the drug is said to produce blood dyscrasia, aplastic anaemia and super infection with overgrowth of *candida* or mucous membranes

Newer, safer derivatives of chloramphenicol derivatives are: *florfenicol*, *thiamphenicol*. The use of chloramphenicol in food animals is banned due to the fact that there is potential to predispose humans to residue-induced aplastic anaemia in humans.

DOSE:

Oral administration

Dog, foal, calf, - 50mg/kg every 12 hours

Cat - 25mg/kg every 12 hours

Parenteral administration

Dog - 50mg/kg I.M, SC slow I.V. every 12 hours

Cat - 25mg/kg I.M. Sc. Or slow I.V. every 12 hours

Horse - 30-50mg/kg I.M. every 12 hours.

Ruminant - 10-25mg/kg I.M. every 12 hours

Pig - 10-25mg/kg I.M. daily

MACROLIDE ANTIBIOTICS

History: Erythromycin which is a prototype macrolide was isolated from *Streptomyces erythreus* in 1952.

Erythromycin was the first of these drugs to find clinical application both as the drug of first choice, and as alternatives to penicillin.

Chemistry: The Macrolides are group of antibiotics with macrocyclic lactone ring to which deoxysugars (desoamines and caldinoses) are attached. Other examples include; oleandomycin, tylosin, carbomycin, spiramycin, tiamulin, tilmicosin.

Newer ones: roxithromycin, and dithromycin.

Mode of action of the drug:

The mechanisms of action of the drug - it inhibits bacterial protein synthesis by binding to the 50s ribosome, preventing translocation of amino acids to the growing peptide.

Antimicrobial spectrum: It is effective against gram positive organisms such as *staphylococci*, *mycoplasma*, *spirochaetes*, and certain mycobacteria are sensitive to the group.

Resistance: Resistance to macrolides can develop rapidly, it may be chromosomal or plasmid – mediated and results from decreased drug binding by the 50s ribosome. This occurs as a result of resistance and Methylase enzymes which alters the ribosomal binding site for erythromycin.

Pharmacokinetics:

The erythromycin is destroyed by gastric acid, thus either enteric coated tablets or stable esterified salts (*stearate, tartrate, estolate or lactobionate*) are administered and allow oral absorption. The Newer ones (macrolides) are stable to gastric acids and are readily absorbed. The drug diffuses throughout the tissues of the organs except those of C.N.S.

The Macrolides accumulates in the macrophages. The Macrolides are concentrated in the lung tissue at levels sixty times higher than serum levels.

Erythromycin is metabolized by the liver and excreted in bile. The remainder is excreted in active form in urine and bile.

Tylosin and tilmicosin are excreted in unchanged in bile and urine.

Azithromycin is primarily concentrated and excreted in active form in the bile. Minor amounts are eliminated in the milk of lactating animals.

Roxithromycin is long acting with a half-life of 12 hours and it is becoming an alternative to erythromycin for respiratory, genital tract, skin and soft tissue infections.

Tylosin – is effective against mycoplasma, and is a drug of choice in mycoplasmosis in poultry, in particular chronic respiratory disease in chickens, an infectious sinusitis in turkey, as well as respiratory infections in small animals and calves. The drug is used in pleuropneumonia in goats; it is used in vibriotic dysentery exudative dermatitis (greasy pig disease) in swine. 100 and 500 gm per ton of feed to improve weight gain by feed conversion efficiency of swine, cattle, and chickens.

Spiramycin: has been added to drinking water for the mass treatment and prevention of mycoplasmosis in chickens and turkey. It is used in treatment of mastitis due to penicillin – resistant staphylococci. In dry –cow mastitis spiramycin – neomycin combinations have been used effectively.

ADVERSE EFFECTS:

Alteration of gastrointestinal flora following biliary excretion.

The effect of distortion of microbial flora is very common in horses and might cause diarrhea.

DOSE:

Veterinary Macrolide preparations are limited to base forms of erythromycin and tylosin for oral and parenteral use.

All Species: 10mg/kg I.M. daily

Dog: erythromycin 15mg/kg P.O. 3 times per day

Swine: tylosin 7mg/kg, in feed; 0.2-0.5gm per litre of water

Poultry: tylosin 0.5gm/litre of drinking water, in turkeys; tylosin may be injected directly into the sinuses.

LINCOSAMIDES :

Lincomycin.

Source:- Lincomycin was isolated from *Streptomyces lincolnensis*, and its semi-synthetic derivative, clindamycin

CHEMISTRY: They are derivatives of a sulphur containing octose with an amino acid- like side chain.

MODE OF ACTION: Same as erythromycin and chloramphenicol.

SPECTRUM OF ACTIVITY: They are effective against gram-positive cocci, anaerobes, Toxoplasma and mycoplasma species.

RESISTANCE: Takes place as a result of altered drug binding by bacterial ribosomes is the usual form of resistance. There is a cross resistance between Lincosamides and macrolides is common.

PHARMACOKINETICS:

Lincomycin is not completely absorbed following oral administration; but clindamycin is well absorbed orally, distribution is wide, with excellent penetration of bone and soft tissues, including tendon sheath. The lincosamides accumulate in neutrophils and macrophages, but CNS levels are low unless the meninges are inflamed clindamycin is extensively protein-bound. Elimination is via hepatic oxidative metabolism primarily, with some excreted unchanged in the urine, bile and faeces. Elimination half-lives are 3-5 hours in dogs and cats.

THERAPEUTIC USES:

Lincomycin has become obsolete clindamycin is used in dogs and cats for periodontal disease, osteomyelitis, dermatitis, and deeps of tissue infections and for treating toxoplasmosis. Lincomycin has been used in swine in the treatment of arthritis and pneumonia involving mycoplasma species. A combination of lincomycin and spectinomycin (an amino- cyclitol) is used in respiratory diseases of cattle due to mycoplasma and pasteurella.

DOSE:

Lincomycin or Clindamycin

Cow, Swin, Dogs, Cats: 10mg/kg 1m, twice a day

Lincomycin

Dog, Cats : 25mg/kg P.O every 12hour

15mg/kg P.O, every 8 hours

22 mg/kg 1m, Sc daily

Pig : Feed –mix: 110 – 220gm/ tones feed

Clindamycin

Dog : 5 – 10 mg/kg P.O every 12 hours

ADVERSE EFFECTS: Lincosamides are relatively safe in dogs and cats.

- Clindamycin may cause local irritation at injection site.
- Serious diarrhea with hemorrhage colitis may occur in horses after low doses. Clindamycin is very toxic in rabbits, guinea pig and hamsters.
- Fatal pseudomembranous colitis due to over growth of Clostridium difficile in the lower bowel, which elaborates necrotizing toxins.

SULPHANAMIDES

HISTORY:-The sulphanamides originated from the dye prontosil which was shown in 1935 by Gerhard Domagk to be effective in VIVO against haemolytic streptococcal infection in mice. He was awarded the 1939 Nobel Prize medicine for his discovery.

Also in 1935, four French scientists, Bovet Nitti, Trefovel and Trefouel demonstrated that the body converted prontosil to Sulphanilamide, which is the active part of the molecule since then the sulphonamide nucleus has been modified. The modifications are designed to achieve greater antibacterial potency, a wider spectrum of activity, greater solubility in urine and a longer duration of action.

In the 1970s, a synergistic combination of sulphamethoxazole with trimethoprim (Co-trimazole)

CHEMISTRY

The sulphonamides are derivatives of P-aminobenzene sulphonic acid and are structurally similar to P-aminobenzoic acid (PABA, an essential member of Vitamin B complex, and an intermediate in bacteria synthesis of folic acid).

- Sulphonamides are insoluble in water
- Sodium salts of sulphonamides are soluble
- Sulphonamides mixtures are used to reduce toxicity and increase solubility in water.
- It is important to note that only sulphonamides that have free or potentially free P-amino group show antibacterial activity