

TETRACYCLINES

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Background

- ✚ Chlortetracycline was discovered in 1944 and marketed for clinical use in 1948. This was followed shortly thereafter with the discovery and marketing of oxytetracycline. These were the first members of the tetracycline family to be approved for clinical use.
- ✚ These molecules, together with the later discovered oxytetracycline and demecloxycline, are products of streptomyces spp. Semi-synthetic derivatives are also available such as: Methacycline, lymecycline, rolitetracycline, doxycycline and minocycline.
- ✚ Tetracyclines are classic broadspectrum antibiotics because of their activity against Gram positive and Gram negative aerobic and anaerobic bacteria, including such organisms as Brucella; Coxiella; Ehrlichia; Anaplasma; some Mycobacterium; Mycoplasma and Rickettsia/Neorickettsia.
- ✚ The extra-ordinarily widespread nature of acquired resistance, which has developed in the many common pathogens and particularly gram negatives, has limited the use of the tetracyclines in many clinical circumstances.
- ✚ Generally, tetracyclines have favorable pharmacokinetic properties, particularly the more lipophilic semisynthetic derivatives.
- ✚ Because of their low cost, and the limited choice of antibacterial agents available, they tend to be used as first line antibiotics in ruminants and swine.
- ✚ With the advent of newer antimicrobial agents and the increasing resistance to tetracyclines, these agents are no longer first choice antibiotics in companion animals or horses.
- ✚ Despite their limitations and restricted use patterns in some animal species, they are still the drug of choice for the treatment of Chlamydia; Ehrlichiosis; Coxiellosis; Rickettsiosis and for some Mycobacterial and Mycoplasmal infections.

Chemistry

- ✚ Tetracyclines are crystalline amphoteric substances that can exist as acid or base salts. They are available for use mainly as the hydrochlorides, in a wide variety of dosage forms, both oral and parenteral.

- ✚ Solutions of the hydrochlorides are acidic and, with the exception of Chlortetracycline, fairly stable.
- ✚ Tetracyclines are strong chelating agents.
- ✚ Their ability to chelate divalent and trivalent metal ions such as calcium may result in tooth discoloration.

Mechanism of Action

- ✚ Tetracyclines are bacteriostatic antibiotics that inhibit protein synthesis in susceptible micro-organisms. After diffusion through the outer cell membrane, an active carrier mediated process transports the drugs through the inner cytoplasmic membrane.
- ✚ Once inside the cell, tetracyclines bind reversibly to receptors on the 30S subunit of the bacterial ribosome where they interfere with the binding of the aminoacyl-transfer RNA to the RNA-ribosome complex. This binding prevents the addition of amino acids to the elongating peptide chain, inhibiting protein synthesis.

Antimicrobial Activity

- ✚ Tetracyclines are classic broad spectrum antibiotics. They exhibit activity against a broad spectrum of Gram positive and Gram negative bacteria including such micro-organisms as Mycoplasma; Ehrlichia; Anaplasma; Chlamydia/Chlamidophila; Rickettsia/Neorickettsia.
- ✚ The spectrum of activity of tetracyclines also encompasses various protozoan parasites such as plasmodium falciparum; Entamoeba histolytica; Giardia lamblia; Leishmania major; Trichomonas spp., and Toxoplasma gondii.
- ✚ Tetracyclines are typically used as the drug class in determining susceptibility. Minocycline, which is the most lipid soluble, has greater activity than other tetracyclines against Nocardia, some Mycobacteria and aerobes.
- ✚ Generally, doxycycline and minocycline are more active against staphylococcus aureus and various streptococci than is tetracycline

Good or Moderate Activity (MIC ≤ 4µg/ml)

- ✚ Tetracyclines, as a group, exhibit good to moderate activity against the following Gram positive aerobes: Bacillus spp. Corynebacterium spp. Erysipelothrix rhusiopathie; Listeria monocytogenes; some Streptococci and against the following Gram negative bacteria: Actinobacillus spp. Bordetella spp. Brucella spp. Francisella tularensis; Haemophilus spp. Lawsonia intracellularis; Pasteurella spp. Including P. multocida; Mannheimia spp. Yersinia spp. Campylobacter fetus; Borrelia spp. Leptospira spp. Mycoplasma spp.

Chlamydial/Chlamidophila spp. Rickettsia/Neorickettsia; Coxiella burnetii; Ehrlichia spp. Anaplasma and some aerobes including Actinomyces spp. and Fusobacterium spp.

Variable susceptibility

- ✚ Because of acquired resistance, many isolates of staphylococci, enterococci; streptococci, Enterobacteriaceae including Enterobacter spp. E.coli; Klebsiella spp. Proteus spp. and Salmonella spp. and anaerobes such as Bacteroides spp. and Clostridium spp. show variable susceptibility.
- ✚ Some isolates of Mannheimia haemolytica may also be resistant to tetracyclines.

Resistant ($MIC \geq 16 \mu g/ml$)

- ✚ Acquired resistance to tetracyclines is widespread among bacteria and Mycoplasma and has considerably reduced the usefulness of these agents.
- ✚ Resistance is extremely rare amongst obligate intracellular pathogens such as: Chlamydia; Chlamydophila; Ehrlichia and Anaplasma.
- ✚ However horizontal transmission of tetracycline resistance was recently demonstrated in Chlamydia suis (Duga et al., 2004).
- ✚ Most tetracycline resistant bacteria carry one or more of the 36 different acquired tetracycline resistance genes (Roberts, 2003). These genes are often on mobile elements such as plasmids; transposons; conjugate transposons and or integrons.
- ✚ Resistance to tetracyclines can be mediated by one of three different mechanisms: (1) An energy dependent efflux of tetracyclines carried out by transmembrane spanning proteins, which results in reduction of the concentration of tetracyclines in the cytosol (2) Ribosomal protection, in which the tetracyclines no longer bind productively to the bacterial ribosome; or (3) Chemical modification, requiring oxygen, NADPH, and catalysis by enzymes.
- ✚ The first two mechanisms are by far the most common.

Pharmacokinetic Properties

- ✚ In dogs and cats, most tetracyclines are adequately absorbed from the gastrointestinal tract, but systemic availability can vary widely among different oral preparations.
- ✚ With the exception of minocycline and doxycycline, the absorption of tetracyclines is decreased by the presence of food, particularly milk and its products, in the stomach.
- ✚ Divalent and trivalent cations such as: Calcium; Magnesium; Iron; Aluminium decrease absorption by chelating tetracyclines.

- ✚ Tetracyclines vary in lipid solubility, and this property largely determines their distribution and rate of excretion.
- ✚ Tetracyclines enter most tissues and body fluids with the exception of cerebrospinal fluid (CSF).
- ✚ The rate at which tetracyclines penetrate the blood brain barrier and blood-CSF barriers is related to their degree of lipid solubility and, to a much lesser extent, plasma protein binding.
- ✚ Minocycline and doxycycline are more lipid soluble than other members of the group and are also more highly bound to plasma proteins. The limited evidence available suggests that the minocycline has greater capacity than other tetracyclines to penetrate cellular barriers, as it attains higher concentrations in poorly accessible fluids such as tears and prostatic fluid.
- ✚ Because tetracyclines have approximately equal antimicrobial activity against most Gram negative bacteria, the higher concentrations attained in tissues by minocycline give this congener greater clinical efficacy.
- ✚ For Gram positive bacteria, minocycline and doxycycline are more active than the other tetracyclines.
- ✚ As a result of chelation with calcium, tetracyclines become bound at active sites of ossification and in developing teeth.
- ✚ The drugs cross the placenta to reach the fetus and are secreted in milk, where they reach concentrations approximating those of serum.
- ✚ Tetracyclines, except minocycline and doxycycline are excreted unchanged in urine, and to a lesser extent, in bile.
- ✚ As glomerular filtration is their mechanism of excretion, impaired renal function can increase their elimination half life.
- ✚ Tetracyclines undergo entero-hepatic circulation, with much of the compound excreted in bile being re-absorbed from the intestines.
- ✚ This process contributes to the half life of 6-10 hours, which is long for drugs that are eliminated mainly by renal excretion.
- ✚ The cumulative recovery of minocycline from urine and feces is much lower than for other tetracyclines, which suggests that this compound is eliminated partly by metabolism.

- ✚ The elimination mechanism for doxycycline differs from that of other tetracyclines in that this agent enters the intestines both by excretion in the bile and directly by diffusion and is excreted in feces.
- ✚ Because doxycycline elimination does not involve renal excretion, it can be used for the treatment of systemic infections in dogs and cats with renal impairment.
- ✚ The bioavailability of orally administered oxytetracycline is 5% compared to 37% for Chlortetracycline in non fasting calves.
- ✚ Bioavailability is further reduced by administration in milk or milk replacer.
- ✚ Serum concentrations of tetracycline are much higher following oral administration to fasted calves. The long acting formulations of oxytetracycline available for IM administration to food animals have their long acting effect because of both the high dosage used and the prolonged drug persistence at the site of IM injection as a result of tissue irritation (Nouws et al., 1990).
- ✚ In swine, the bioavailability of most orally administered tetracyclines is poor.
- ✚ Because of this, and the fact that tetracyclines are time dependent drugs, the achievable serum concentrations are only adequate for treating the most susceptible organisms following administration in food or water.
- ✚ However, because of increased rate of absorption, therapeutic concentrations of doxycycline or minocycline may be reached by administration of high concentration of the drug in feed.
- ✚ The pharmacokinetics of IV and IM oxytetracycline and oral doxycycline have been studied in horses. IV administration of oxytetracycline is preferred over IM administration because it results in higher and more persistent serum concentration.
- ✚ The usefulness of oral doxycycline in horses is limited due to the low serum concentrations achieved presumably as a result of poor oral bioavailability of the drug.
- ✚ For example, the average peak serum concentration in horses following multiple administrations of a dose of 10mg/kg bdw at 12h intervals is only 0.46µg/ml. This is in contrast to peak serum concentrations of 3.5µg/ml in dogs receiving a dose of 5mg/kg bdw. Concentration in synovial and peritoneal fluids of horses are similar to peak serum concentration, while the drug cannot be detected in CSF.
- ✚ Endometrial tissue concentration are slightly higher than serum concentration while concentration in urine range between 75 and 145µg/ml.

Drug Interactions

- ✚ Absorption of tetracyclines is impaired by antacids containing aluminium, calcium or magnesium, by iron containing preparations and by bismuth subsalicylate.
- ✚ Synergism between tetracyclines and tylosin against *Pasteurella* has been described and may occur with other macrolides and other bacteria.
- ✚ Combination with polymyxins may also give synergistic effects by enhancing bacterial uptake of the drugs.
- ✚ Doxycycline is synergistic with rifampin or streptomycin in treatment of brucellosis.
- ✚ Doxycycline has been found to be synergistic with pyrimethamine in the effective treatment of toxoplasmosis in experimentally infected mice.

Toxicity and Adverse Effects

- ✚ From a pharmacologic view point, the tetracyclines are relatively safe drugs. Adverse effects may be attributed to their severely irritant nature (vomiting after oral administration, tissue damage at injection site); their disturbance of intestinal flora; their ability to bind calcium (cardiovascular effects, deposition in teeth and bone); and their toxic effects on liver and kidney cells.
- ✚ Fatal anaphylaxis has occasionally been recorded.
- ✚ Unless administered slowly, IV injection of a tetracycline is likely to cause an animal to collapse. It is postulated that, this is due to the cardiovascular effect of the high initial concentration in the systemic circulation.
- ✚ Tetracyclines induce dose related functional changes in renal tubules in several species (Riond and Riviere, 1989).
- ✚ Tetracycline induced renal toxicosis may be exacerbated by dehydration, hemoglobinuria, myoglobinuria, toxemia or the presence of other nephrotoxic drugs (Riond and Riviere, 1989).
- ✚ Severe liver damage can follow overdosage of tetracyclines in animals with pre-existing renal failure and may also be associated with late pregnancy.
- ✚ In cattle, high doses (33mg/kg bdw IV) have led to fatty infiltration of the liver and severe proximal renal tubule necrosis (Griffin et al., 1979).
- ✚ Tetracyclines should be administered to cattle only in recommended doses to avoid problems of nephrotoxicosis (Lairmore et al., 1984).
- ✚ Transient hemoglobinuria with trembling and sub-normal temperature lasting four hours has been reported with long acting formulations (Anderson, 1983).

- ✚ Mal-absorption because of moderate diarrhea may occur in calves after oral administration of therapeutic doses.
- ✚ I.V injections of all forms of tetracyclines should be given slowly to cattle over a period of not less than five minutes (Gyrd-Hensen et al., 1981).
- ✚ In horses, the most feared side effect of tetracycline is enterocolitis due to alteration of intestinal microflora and super infection with resistant salmonella or unidentified pathogens which may include Clostridium difficile or C.perfringens.
- ✚ I.V administration of doxycycline to horses results in cardiovascular collapse and death, even when slow I.V infusions are used.
- ✚ Nephrotoxicosis has been reported especially in foals receiving high doses for the treatment of contracted tendons.
- ✚ In dogs, fatal nephrotoxicosis has been reported after the I.V administration of tetracyclines at higher than recommended doses.
- ✚ Administration to growing puppies or pregnant bitches results in yellow discoloration, of primary and to a lesser extent, permanent teeth.
- ✚ Oxytetracycline irritates tissues.
- ✚ The long acting 20% formulations are particularly irritating. The prolonged action is related to delayed release and hence is associated with increased irritation.
- ✚ Tetracyclines have anti-anabolic effects that may produce azotemia. Such effects can be exacerbated by corticosteroids.
- ✚ Tetracyclines may also cause metabolic acidosis and electrolyte imbalance

Administration and Dosage

- ✚ Tetracyclines are available in capsular and tablet forms and are usually administered PO to dogs and cats. Milk, antacids and ferrous sulphate interfere with absorption.
- ✚ Because of poor water solubility, oxytetracycline dihydrate must be given in much higher doses than the hydrochloride to produce equivalent tissue concentration.
- ✚ I.M injection of tetracycline cannot be recommended for horses or companion animals because of local tissue damage and pain, and erratic absorption.
- ✚ The recommended dose in cattle is 10mg/kg given IM or preferably IV, because of variability in absorption. The long acting oxytetracycline parenteral preparation, which is oxytetracycline base in 2-pyrrolidone, is approved for IM use in cattle and swine only.

- ✚ A single IM dose of 20mg/kg provides serum concentration of oxytetracycline above 0.5µg/ml for 48 hours but appears to offer no advantage over the same dose of the conventional drug IM (Nouws, 1986).
- ✚ SC injection in cattle maintain similar serum concentration to those following IM administration and appears to be better tolerated.
- ✚ To prevent adverse effects, it is important to differentiate between the conventional and the long acting formulation in dosage decisions

Clinical Applications

- ✚ The primary indications for tetracyclines are in the treatment of borreliosis, brucellosis, chlamydiosis, ehrlichiosis, leptospirosis, listeriosis, rickettiosis and tularemia.
- ✚ Tetracyclines have been used for many years in managing infectious diseases in food animals because of their low cost, broad antimicrobial activity, ease of administration and general effectiveness.
- ✚ However, their widespread use has undoubtedly contributed to resistance in important pathogenic bacteria, which now limits their use.
- ✚ The tetracycline capacity to attain effective concentration in most tissues, except those separated by specialized cellular barriers, together with their broad spectrum of activity, makes them particularly useful in the treatment of mixed bacterial infections.
- ✚ The activity of the agents against Rickettsia, Chlamydia, Ehrlichia and some Mycoplasma makes them the drugs of choice in treatment of infections caused by these micro-organisms.
- ✚ One disadvantage of tetracyclines over a number of other antimicrobial drugs is their bacteriostatic action, so the treatment may need to be continued for longer than with bactericidal drugs.
- ✚ Tetracyclines are commonly used in the treatment of brucellosis, usually in combination with rifampin or streptomycin.
- ✚ Minocycline and doxycycline, could be used in the treatment of infections caused by intracellular bacteria, including ehrlichia and coxiella.

