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Popular Article

The pharmacological perspectives of Tetracyclines in Veterinary Medicine

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History

Tetracycline antibiotics were produced by systemic screening of soil microorganisms. The first member of the group was chlortetracycline derived from soil actinomycete *Streptomyces aureofaciens* introduced in 1948. This was followed by oxytetracycline. Removal of chlorine atoms from chlortetracycline produced semi-synthetic tetracycline introduced in 1952. The further discovery led to other semi-synthetic tetracyclines like metacycline, doxycycline and rolitetracycline. Doxycycline and minocycline are relatively newer tetracyclines with high lipid solubility and a longer duration of action. In 2005, tigecycline, the first member of a new subgroup of tetracyclines named glycylcyclines, was introduced to treat infections that areresistant to other antimicrobials including conventional tetracyclines.

Classification

Tetracyclines are generally classified according to theirduration of action.

1. Short-acting tetracyclines (t1/2= <8 hours)

ex. oxytetracycline, tetracycline and chlortetracycline.

2. Intermediate acting tetracyclines (t½ = 8-16 hours)ex. demecibeline and metacycline.
3. Long-acting tetracyclines (t½=>16 hours) ex. doxycycline, minocycline and tigecycline.

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Mechanism of action

Tetracyclines inhibit bacterial protein synthesis and are primarily (bacteriostatic) In a way somewhat similar to aminoglycosides, the action of tetracyclines can be dividedinto two processes - passage of tetracyclines into bacterial cell and interaction of tetracyclines with bacterial ribosomes.

Passage into bacterial cell

Tetracyclines can enter gram-negative bacteria through two mechanisms: passive diffusion through porin channelsin the outer cell membrane or direct passive diffusion through the lipid bilayer for morelipid-soluble members.

An energy-dependent active transport system is also usedto pump tetracyclines across the cytoplasmic membrane. The process of tetracycline entry into gram-positive bacteria is not well understood, but it requires an energy-dependent carrier transport mechanism.

Interaction with bacterial ribosomes

Once inside the bacterial cell, tetracyclines bind to the 30S ribosomal subunit and prevent aminoacyl t-RNA from accessing the acceptor site on the mRNA-ribosome complex. This leads to the inhibition of protein synthesis bypreventing the addition of amino acids to the growing peptide chain. Tetracyclines are effective against multiplying microorganisms, more active at pH 6-6.5, and primarilybacteriostatic.

Their effects are reversible upon drug removal, requiring aresponsive host-defense system to remove static bacteria.At high concentrations, they can become bactericidal and affect the functional integrity of bacterial cell membranes,as well as impair protein synthesis in host cells. Tetracyclines have poor penetration into eukaryotic cells due to lacking a specific carrier transport system, and the mammalian protein synthesizing apparatus is less sensitiveto them.

Pharmacokinetics

Absorption

Tetracyclines can be administered orally, parenterally, andtopically.

Oral administration in carnivores results in rapid absorptionfrom the gastrointestinal tract, with peak plasma concentrations reached within 2-4 hours, persisting for 6-8hours. The absorption of tetracyclines can be interfered with bymilk, milk products, calcium, magnesium, iron or iron preparations, and antacids, due to chelation, except for doxycycline and minocycline, which have

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high lipid solubility. Tetracyclines should not be given orally to ruminants asthey are poorly absorbed and can disrupt ruminal microflora. The oral absorption of tetracyclines is variable with olderdrugs (e.g. chlortetracycline) being less bioavailable andnewer lipid soluble tetracyclines (e.g. minocycline and doxycycline) being 100% bioavailable.

T $_{1/2}$ of tetracyclines Tetracycline: 6-12 hours, Doxycycline: 18-22 hours Minocycline: 16-22 hours

Distribution

Tetracyclines bind to plasma proteins to varying degreesand are widely distributed in most tissues including kidneys, liver, lungs, bile and bones. However, with the exception of lipid soluble members (e.g.doxycycline and minocycline), tetracyclines do not penetrate the brain and CSF. Tetracyclines are stored in the reticuloendothelial cells ofliver, spleen and bone marrow. They are also incorporated into forming bone and enameland dentine of unerupted teeth possibly because of their binding action with Ca^{++}. Tetracyclines cross the placenta and enter foetal circulationand amniotic fluid.

Biotransformation and excretion

With the exception of lipid-soluble tetracyclines, the tetracycline antibiotics are not metabolized to a significantextent in the body. Most tetracyclines are excreted in urine (~60%) via the glomerular filtration pathway and in faeces (-40%) viabiliary excretion. Tetracyclines undergo enterohepatic circulation, which may affect their duration of action. Doxycycline is largely excreted through the GI tract

Spectrum of action

The tetracyclines are broad-spectrum antibiotics. They are active against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria. They are also active against Mycoplasma, Rickettsia, Chlamydia and some protozoa like *Anaplasma, haemobartonella* and amoebae. When originally introduced, they affected practically all types ofbacteria. Presently, strains of Pseudomonas aeruginosa, Proteus, Serratia, Klebsiella, Salmonella, Staphylococcus and Corynebacterium species appear to have become resistant to tetracyclines. Tetracyclines are ineffective against fungi and viruses.

Clinical uses

- Tetracyclines are used to treat bacterial infections in animals and humans, including respiratory diseases, borreliosis, brucellosis, chlamydiosis, and rickettsiosis.

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- They are effective against mixed bacterial infections andobligate intracellular pathogens.
- The newer tetracyclines, like minocycline and doxycycline, have better cell and are also lipophilic, which means that theycan attain concentrations in sites such as the prostate, which are poorly accessible to older members of the group.
- Tetracyclines are commonly used in combination with other drugs, like rifampin or streptomycin, and treatment may needto be longer than with bactericidal drugs due to their bacteriostatic.
- However, the widespread use of tetracyclines in food animals has contributed to very widespread resistance in pathogenic bacteria, including Enterobacteriaceae and other important pathogens. As a result, tetracyclines should be used judiciouslyto minimize the development of antibiotic resistance.

Cattle, Sheep and Goat

- Tetracyclines treat and prevent bovine pneumonia, but resistancelimits effectiveness
- Long-acting parenteral formulations effective in treating respiratorydisease in cattle, sheep, and goats
- Oral tetracycline administration in water not recommended forfeedlot cattle pneumonia prophylaxis
- Parenteral administration more effective for feedlot pneumoniaprophylaxis
- Tetracyclines treat clostridial infections, listeriosis (10 mg/kg/day IV recommended for neural listeriosis)
- Minocycline is an alternative to ampicillin in human medicine Tetracyclines effective in treating and preventing various cattleinfections
- Oxytetracycline is the drug of choice for acute *Anaplasma marginale* Infections
- Tetracyclines can prevent *Babesia bovis* and *B. bigemina* and treatheartwater disease caused by *Ehrlichia ruminantium*
- Used for prophylaxis against East Coast fever caused by *Theileria parva* and tickborne fever caused by *Anaplasma phagocytophilum*.

Horses

- The use of oxytetracycline in horses has been controversial due to early reports of enterocolitis, but most treated horses don't exhibit side effects.
- Tetracyclines have a limited spectrum against common equinepathogens and can be irritant when injected.
- Oxytetracycline is effective against non-enteric Gram-negative bacteria and about 70% of Staphylococcus spp., but only 50-60% ofEnterobacteriaceae and β-hemolytic streptococci.
- Doxycycline is safe for oral administration in horses but has poorbioavailability.
- Oxytetracycline or doxycycline are preferred for *A. phagocytophilum*, *B. burgdorferi*, and *N. risticii* infections in horses.
- Oxytetracycline is effective against *A. phagocytophilum* and *N.risticii* infections in horses

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and has been successful in treating Lawsonia infection in foals.

- Oxytetracycline has been found more effective than doxycycline orceftiofur in eliminating persistent *B. burgdorferi* infection in ponies.

Dogs and cats

- Tetracyclines are the drugs of choice for *A. phagocytophilum,Ehrlichia canis*, and *Rickettsia rickettsii* infections in dogs.
- Doxycycline is effective in preventing and treating acute illnesscaused by *R. rickettsii* but may not remove the carrier state.
- Minocycline co-administered with streptomycin is the mosteffective treatment for *Brucella canis* infection in dogs.
- Tetracycline hydrochloride is successful in treating P. aeruginosaurinary tract infections in dogs.
- Tetracyclines are used in dogs to treat Lyme borreliosis, leptospirosis, periodontitis, superficial pyoderma, and deeppyoderma.
- Cats with *Chlamydophila felis* infection should be treated with tetracyclines for 14 days to eliminate the organism and remove thecarrier state.
- Tetracyclines are drugs of choice for the treatment *of Mycoplasma haemofelis* in cats.
- Prolonged oral treatment with doxycycline does not eliminate thecarrier state in *Bartonella henselae* or *B. clarridgeae* infection in cats.
- Tetracycline treatment of a cat with *Yersinia pestis* infection wasonly temporarily effective.

Poultry

- Tetracyclines are effective in treating chlamydophilosis ifadministered for prolonged periods
- Tetracycline or chlortetracycline can be administered in 1%medicated feed for 45 days
- Doxycycline has been administered at 100 mg/kg IM at 5-dayintervals on 6 or 7 occasions or orally twice daily for 20 days
- Tetracyclines are used in the treatment of chronic respiratory disease (*Mycoplasma gallisepticum*) and infectious synovitis (*Mycoplasma synoviae*), as well as of fowl cholera (P. multocida)
- Prolonged administration of oxytetracycline (250 ppm) in feed isrequired to control *M. gallisepticum* infection in birds
- Tetracycline sorbate has shown efficacy in the oral treatment of naturally occurring *Aspergillus fumigatus* infection.

Non-Antibiotic uses

- Tetracyclines have non-antibiotic effects documented for second and third-generation molecules

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- These effects include anti-inflammatory, immunosuppression, inhibition of lipase and collagenase, antinociceptive, antiosteoporotic, and wound-healing effects
- Tetracyclines protect mice from endotoxin-induced shock by reducing inflammatory cytokine and nitric oxide production
- Minocycline is neuroprotective in many experimental models of neurodegenerative diseases, CNS injury, and viral encephalitis dueto its antiapoptotic and ROS-scavenging properties
- Tetracyclines' matrix-metalloproteinase inhibitory effects havebeen shown to be beneficial for various conditions such as rheumatoid arthritis, gingivitis, acute lung injury, myocardial disease, and cancer
- Intravenous administration of high doses of oxytetracycline to foals may result in acute renal failure, and caution should be taken in foals with preexisting renal damage or hypovolemia, or unable tonurse sufficiently.

Adverse Reactions and Toxicity

- Alteration in microflora in rumen or intestines following oral use leads to digestive disturbances and ruminal stasis and decrease insynthesis and availability of vitamin B and K, particularly in monogastric animals.
- Superinfections by fungi, yeasts, and resistant bacteria maycause severe or fatal diarrhea (in horses) following oral or parenteral administration.
- Tetracyclines are deposited in growing teeth and bones and should not be used in growing animals because they cause yellowishand later brownish discoloration of teeth and suppress bone growth.
- Tetracycline should not be used with immunization programs (as they cause immunosuppression).
- Intramammary infusion of chlortetracycline is contraindicated indry cows (it can cause severe fissure formation and subsequent fibrosis). If infused, cows may fail to lactate after parturition due toteat and udder tissue damage.
- Intra-articular injections of tetracyclines are contraindicated (as they can cause severe irritation).
- If administered by rapid IV injection, hypotension and acute collapse may occur in cattle and horses due to chelation of bloodcalcium. This can be avoided by slow infusion of the drug or pretreatment with IV calcium gluconate.
- Tetracyclines in high doses can produce hepatotoxicity, particularly in pregnant animals or those with renal abnormalities.
- All tetracyclines in high doses are potentially nephrotoxic (due totheir anti-anabolic effect and decrease in host protein synthesis), except doxycycline, and are contraindicated in renal insufficiency.

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- Phototoxic dermatitis is most common with demeclocycline anddoxycycline in humans, but is rare in animals. Hypersensitivity isalso rare.
- In humans, ingestion of outdated tetracyclines can produce a syndrome characterized by aminoaciduria, glycosuria, pyuria, and polydipsia due to proximal convoluted tubular damage (Fanconi syndrome).
- Demeclocycline induces diuresis through its antagonism ofantidiuretic hormone (ADH).

Contraindications

- Tetracyclines are contraindicated in hepatic insufficiency, renaldiseases, and in patients who are hypersensitive to them.
- Oral administration of tetracyclines to ruminants and horses is notrecommended because they inhibit the normal bacterial fermentation of plant fibers.
- Tetracyclines should not be used in the last 2-3 months of gestation in pregnant animals and up to 4 weeks in neonates.
- Tetracycline preparations should never be used beyond their expirydate because they cause damage to the proximal renal tubule due to the formation of a degradation product, anhydro-4-epitetracyclinecausing Fanconi syndrome.
- Tetracyclines should never be administered with food, milk, and milk products because they bind with food particles and also easilywith magnesium, aluminum, iron, and calcium in food and milk products, thereby forming insoluble complexes, which reduce the absorption ability of tetracyclines.
- Oral tetracyclines are generally given at least 1-2 hours before orafter food and milk or any cation-containing product, except for doxycycline and minocycline which may be taken with food (thoughnot with iron, antacids, or calcium supplements).
- Tetracyclines should not be given intrathecally.

Drug interactions

- Antacids containing Al^{3+} or other multivalent cations, iron-containing preparations, and bismuth subsalicylate impair theabsorption of tetracyclines.
- Synergism between tetracyclines and tylosin or tiamulin against respiratory pathogens, including Mycoplasma and Pasteurella, has been reported, and similar effects may occur with other macrolidesand bacteria.
- Combination with polymyxins can enhance bacterial uptake of thedrugs and produce synergistic effects.
- Doxycycline is synergistic with rifampin or streptomycin in treatingbrucellosis.
- Doxycycline was effective in combination with pyrimethamine intreating toxoplasmosis in experimentally infected mice.

Dosage

- Tetracycline and oxytetracycline: Dog & Cat 20 mg/kg orally at 12 hr intervals; 7-10 mg/kg/day IM or IV once a day.

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- Oxytetracycline: Calf, foal, lamb & pig: 10-20 mg/kg orally at 12 hrintervals;
- Horse, foal, cattle, calf, sheep, lamb & pig: 5-10 mg/kg IM orIVonce a day.
- Doxycycline: Small animals: 5-10 mg/kg orally once a day, 5 mg/kgIM or IV once a day.
- Withdrawal periods: Oxytetracycline: Cattle & Pig: 22 days;Poultry: 5 days;
- Oxytetracycline (long acting): cattle-28 days; Chlortetracycline: Cattle: 10 days; Pig: 7 days; Oxytetracyclines are not to be used in lactating cows.

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