

PRODUCT INFORMATION

ACHROMYCIN

DESCRIPTION

Composition ACHROMYCIN : Tetracycline hydrochloride

Tetracycline HCl is a broad spectrum antibiotic isolated from *Streptomyces aureofaciens*. It is a yellow, crystalline, hygroscopic powder soluble 1 in 10 parts of water.

CLINICAL PHARMACOLOGY

Tetracycline is rapidly but incompletely absorbed from the stomach and small intestine. Absorption is impaired by administration with food, milk, antacids and di- and trivalent cations.

A single dose of 250 mg produces a peak serum level of 1-2 mg/L in 2-4 hours. The administration of 250 mg every 6 hours for 24 hours produces a peak plasma concentration of approximately 3 mg/L. The administration of 500 mg every 6 hours produces serum levels of 4-5 mg/L. Doses larger than 500 mg every 6 hours usually do not result in higher serum levels, due to diminished absorption.

Most of the absorbed dose of tetracycline is eliminated unchanged in urine and bile. The remainder, a relatively small amount, is metabolised in the liver. Urinary excretion accounts for approximately 20% of the orally administered dose; the unabsorbed fraction is excreted in the faeces.

The protein binding of tetracycline ranges from 24 to 64%.

MICROBIOLOGY AND INDICATIONS

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis.

Tetracyclines are active against a wide range of Gram-negative and Gram-positive organisms. The drugs in the tetracycline class have similar antimicrobial spectra and cross resistance among them is common.

Indications: Tetracycline hydrochloride is indicated in infections caused by the following micro organisms: Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox, tick fever). *Mycoplasma pneumoniae* (PPLO, Eaton agent). Agents of psittacosis. Agents of lymphogranuloma venereum and granuloma inguinale. The spirochaetal agent of relapsing fever (*Borrelia recurrentis*).

The following Gram-negative micro organism: *Haemophilus ducreyi* (chancroid), *Pasteurella pestis* and *Pasteurella tularensis*, *Bartonella bacilliformis*, *Bacteroides* species, *Vibrio comma* and *Vibrio foetus*. *Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of micro organisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended prior to initiation of therapy.

Tetracycline may be used for treatment of infections caused by the following Gram-negative micro organisms only when bacteriological testing indicates appropriate susceptibility to the drug: *Escherichia coli*, *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*), *Shigella* species, *Mima* species and *Herellea* species, *Haemophilus influenzae* (respiratory infections), *Klebsiella* species (respiratory and urinary infections).

Tetracycline may be used for the treatment of infections caused by the following Gram-positive micro organisms when bacteriological testing indicates appropriate susceptibility to the drug:

Streptococcus species: Up to 44% of strains of *Streptococcus pyogenes* and 74% of *Streptococcus faecalis* have been found to be resistant to tetracyclines. Therefore, tetracycline should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive. For upper respiratory infection due to group A β -haemolytic streptococci (*Streptococcus pyogenes*), penicillin is the usual drug of choice, including prophylaxis of rheumatic fever. *Streptococcus pneumoniae*, *Staphylococcus aureus* in skin and soft tissue infections.

Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to: *Treponema pallidum* and *Treponema pertenue* (syphilis and yaws), *Listeria monocytogenes*, *Clostridium* species, *Bacillus anthracis*, *Fusobacterium fusiforme* (Vincent's infection), *Actinomyces* species.

In acute intestinal amoebiasis, the tetracyclines may be a useful adjunct to amoebicides. In severe acne, the tetracyclines may be useful adjunctive therapy.

Tetracycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral tetracyclines or with a combination of oral and topical agents.

SUSCEPTIBILITY TESTING

Micro organisms may be considered susceptible if the MIC (minimum inhibitory concentration) is not more than 4 $\mu\text{g}/\text{mL}$ and intermediate if the MIC is 4 to 12.5 $\mu\text{g}/\text{mL}$.

Susceptibility plate testing: A tetracycline disc may be used to determine microbial

susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disc susceptibility testing is used a 30 µg tetracycline HCl disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.

CONTRAINDICATIONS

In persons who have shown hypersensitivity to any of the tetracyclines.

Severe renal insufficiency.

Systemic lupus erythematosus.

WARNINGS

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated and, if therapy is prolonged, serum level determinations of the drug may be advisable.

The anti anabolic action of the tetracyclines may cause an increase in BUN. This effect may be enhanced by diuretics.

In patients with significantly impaired function, higher serum levels of tetracycline may lead to azotaemia, hyperphosphataemia and acidosis.

The use of tetracyclines during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow/grey/brown). This adverse reaction is more common during long term use of the drugs, but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group, unless other drugs are not likely to be effective or are contraindicated.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracycline. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs and treatment should be discontinued at the first evidence of skin erythema.

Patients should be advised to avoid direct sunlight or UV light exposure if possible.

The use of tetracycline can cause severe enterocolitis due to resistant staphylococci. Antibiotic associated Pseudomembranous colitis has been reported with many antibiotics including tetracycline. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *C. difficile* should

be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs that delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Use in Pregnancy

Pregnancy Category D

Tetracyclines are safe for use during the first 18 weeks (16 weeks post conception) of pregnancy, after which they cause discolouration of the baby's teeth. During the period of mineralisation of teeth (the second and third trimesters of pregnancy, the neonatal period and the first 8 years of life), tetracyclines may induce hypoplasia of the enamel and discolouration of the teeth. Tetracyclines also accumulate in the growing skeleton. These products should be avoided during the second and third trimesters of pregnancy. (See above WARNINGS about use during tooth development.)

Safe use in pregnancy has not been established. Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

High doses of tetracycline, especially if given intravenously, have been reported to cause severe fatty necrosis of the liver. Because of this and the effect on foetal bone and tooth development, tetracycline should not be given after the first 18 weeks of pregnancy.

Use in Lactation

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Use in Newborns, Infants and Children

(See above WARNINGS about use during tooth development.) All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

PRECAUTIONS

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. In long term therapy, periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies should be performed.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

In venereal diseases when co-existent syphilis is suspected, darkfield examination should be done before treatment is started and the blood seriology repeated monthly for at least 4 months.

Tetracycline is not the drug of choice in the treatment of any type of staphylococcal infection.

If tetracycline is used for the treatment of infections due to group A β -haemolytic streptococci (*Streptococcus pyogenes*) (see INDICATIONS), treatment should continue for 10 days.

ADVERSE REACTIONS

Gastrointestinal: Anorexia, nausea, vomiting, diarrhoea, glossitis, dysphagia, enterocolitis, pancreatitis and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rarely, oesophagitis and oesophageal ulceration.

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Lesions occurring on the glans penis have caused balanitis. Photosensitivity is discussed above. (See WARNINGS).

Dental: Discolouration of teeth (yellow-grey-brown) and/or enamel hypoplasia have been reported in infancy and childhood to the age of 8 years.

Renal toxicity: Rise in BUN has been reported and is apparently dose related (see WARNINGS). Tetracycline may aggravate pre-existing renal failure. Nephrotoxicity has also occurred in association with “acute fatty liver” related to the use of tetracycline in high doses. Degraded tetracycline may result in renal tubular damage and a “Fanconi-like” syndrome.

Hypersensitivity reactions: Urticaria, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus.

Blood: Haemolytic anaemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

Superinfections: As with other antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

CNS: Pseudotumour cerebri (benign intracranial hypertension) in adults has been associated with the use of tetracyclines. The usual clinical manifestations are headache and blurred vision. Bulging fontanelles have been associated with the use of tetracyclines in infants. While both of these conditions and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility for permanent sequelae exists.

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of the thyroid glands. No abnormalities of thyroid function studies are known to occur.

INTERACTIONS

Since tetracyclines may depress plasma prothrombin activity, patients who are on

anticoagulant therapy may require downward adjustment of their anticoagulant dosage. Antacids containing aluminium, calcium or magnesium and preparations containing iron, impair absorption and should not be given to patients taking oral tetracycline.

Foods and some dairy products also interfere with absorption. Oral forms of tetracycline should be given 1 hour before or 2 hours after meals. Paediatric oral dosage forms should not be given with milk formulas and should be given at least 1 hour prior to feeding.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

Reduced efficacy and increased incidence of breakthrough bleeding has been suggested with concomitant use of tetracycline and oral contraceptive preparations.

DOSAGE AND ADMINISTRATION

Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

Patients with renal impairment: (See WARNINGS) Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

Treatment of streptococcal infections: If tetracycline is used for streptococcal infections, therapeutic doses should be administered for at least 10 days.

Adults: Usual daily dose, 1 to 2 g divided into four equal doses, depending on the severity of the infection.

Children: (See WARNINGS) Tetracyclines are not recommended in children 8 years of age or less. For children above the age of 8 years, the usual daily dose is 25 to 50 mg/kg of bodyweight divided into four equal doses. The total dose should not exceed that recommended for adults.

Brucellosis: 500 mg tetracycline four times daily for 3 weeks accompanied by streptomycin, 1 g intramuscularly twice daily the first week and once daily the second week.

Syphilis: A total of 30 to 40 g in equally divided doses over a period of 10 to 15 days should be given. Close follow up, including laboratory tests, is recommended.

PRESENTATION

ACHROMYCIN capsules, 250 mg (orange, marked Sigma 250 mg): 24's

SPONSOR

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