

## Tetracycline

### Physical And Pharmaceutical Properties

Name Status: BAN, rINN

Synonyms: Tetraciclina; Tetraciklin; Tetraciklinas; Tétracycline; Tetracyclinum; Tetracyklin; Tetrasykliini

Chemical Name: A variably hydrated form of (4S,4aS,5aS,6S,12aS)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide

**Molecular Formula:** C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>8</sub>

**Molecular Weight:** 444.4

CAS Registry: 60-54-8 (anhydrous tetracycline); 6416-04-2 (tetracycline trihydrate) Pharmacopoeias: In Eur. (see About Martindale) and US.

**Ph. Eur. 5.5 (Tetracycline).** A yellow crystalline powder. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone. It dissolves in dilute acid and alkaline solutions. A 1% suspension in water has a pH of 3.5 to 6.0. Protect from light.

**USP 29 (Tetracycline).** A yellow, odourless, crystalline powder. It darkens in strong sunlight. Soluble 1 in 2500 of water and 1 in 50 of alcohol; practically insoluble in chloroform and in ether; soluble in methyl alcohol; freely soluble in dilute acids and in alkali hydroxide solutions. It loses not more than 13% of its weight on drying. A 1% suspension in water has a pH of 3.0 to 7.0. The potency of tetracycline is reduced in solutions having a pH below 2 and it is rapidly destroyed in solutions of alkali hydroxides. Store in airtight containers.

**Protect from light. ATC: A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02**

## Tetracycline Hydrochloride

### Physical And Pharmaceutical Properties

Name Status: BANM, rINNM

Synonyms: Hidrocloruro de tetraciclina; Tetraciclina, hidrocloruro de; Tetraciklinhidroklorid; Tetraciklino hidrochloridas; Tétracycline, Chlorhydrate de; Tetracyclini Hydrochloridum; Tetracyklin hydrochlorid; Tetracyklinhidroklorid; Tetrasykliinihidrokloridi

**Molecular Formula:** C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>8</sub>.HCl

**Molecular Weight:** 480.9

CAS Registry: 64-75-5

Pharmacopoeias: In Chin., Eur. (see About Martindale), Int., Jpn, Pol., US, and Viet.

US also includes Epitetracycline Hydrochloride.

**Ph. Eur. 5.5 (Tetracycline Hydrochloride).** A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone. It dissolves in solutions of alkali hydroxides and carbonates. Solutions in water become turbid on standing, owing to the precipitation of tetracycline. A 1% solution in water has a pH of 1.8 to 2.8. Protect from light.

**USP 29 (Tetracycline Hydrochloride).** A yellow, odourless, hygroscopic, crystalline, powder. Tetracycline hydrochloride darkens in moist air when exposed to strong sunlight. Soluble 1 in 10 of water and 1 in 100 of alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates, although it is rapidly destroyed by alkali hydroxide solutions. A 1% solution in water has a pH of 1.8 to 2.8. The potency of tetracycline hydrochloride is reduced in solutions having a pH below 2. Store in airtight containers. Protect from light. ATC: A01AB13; D06AA04; J01AA07; S01AA09; S02AA08; S03AA02

### Incompatibility.

Tetracycline injections have an acid pH and incompatibility may reasonably be expected with alkaline preparations, or with drugs unstable at low pH. Tetracyclines can chelate metal cations to produce insoluble complexes, and incompatibility has been reported with solutions containing metallic salts. Reports of incompatibility are not always consistent, and other factors, such as the strength and composition of the vehicles used, may play a role.

### Stability.

Tetracycline undergoes reversible epimerisation in solution to the less active 4-epitetracycline;<sup>1,2</sup> the degree of epimerisation is dependent on pH, and is greatest at a pH of about 3, with conversion of some 55% to the epimer at equilibrium.<sup>1</sup> The rate at which epimerisation occurs is affected by a variety of factors including temperature and the presence of phosphate or citrate ions.<sup>1</sup> Intravenous solutions of tetracycline hydrochloride with a pH between 3 and 5 have been reported to be stable for 6 hours, but to lose approximately 8 to 12% of their potency in 24 hours at room temperature.<sup>3</sup> Although epimerisation has been observed to be the dominant degradation reaction at pH 2.5 to 5, outside this pH range other reactions become important, with the pH-dependent formation of anhydrotetracycline at very low pH, and oxidation to isotetracycline at alkaline pH.<sup>4</sup>

In contrast to the case in solution, suspensions of tetracycline hydrochloride with a pH between 4 and 7 are stable for at least 3 months.<sup>2</sup> This is because epimerisation, which continues until an equilibrium is achieved between tetracycline and its epimer, depends only on the portion in solution, and the solubility of tetracycline at this pH range is low.

The stability of solid dosage forms and powder at various temperatures and humidities has also been studied; tetracycline hydrochloride was fairly stable when stored at 37° and 66% humidity for 2 months, with about a 10% loss of potency, but the phosphate was rather less stable, with potency losses of 25 to 40% and the formation of potentially toxic degradation products.<sup>5</sup> Comparison with other tetracyclines indicated that tetracycline was less stable than demeclocycline and more stable than rolitetracycline.<sup>5</sup> However, although this study, and an accelerated stability study carried out by WHO<sup>6</sup> indicate that there is a risk of deterioration of solid dose tetracycline, in practice a study of its stability during shipment to the tropics found that deterioration was not a problem.<sup>7</sup> 1. Remmers EG, et al. Some observations on the kinetics of the C4 epimerization of tetracycline. *J Pharm Sci* 1963; 52: 752-6.

2. Grobber-Verpoorten A, et al. Determination of the stability of tetracycline suspensions by high performance liquid chromatography. *Pharm Weekbl (Sci)* 1985; 7: 104-8. (PubMed id:4022761)

3. Parker EA. Solution additive chemical incompatibility study. *Am J Hosp Pharm* 1967; 24: 434-9. (PubMed id:6075728)

4. Vej-Hansen B, Bundgaard H. Kinetic study of factors affecting the stability of tetracycline in aqueous solution. *Arch Pharm Chemi (Sci)* 1978; 6: 201-14.

5. Walton VC, et al. Anhydrotetracycline and 4-epianhydrotetracycline in market tetracyclines and aged tetracycline products. *J Pharm Sci* 1970; 59: 1160-4. (PubMed id:4989725)

6. WHO. WHO expert committee on specifications for pharmaceutical preparations: thirty-first report. WHO Tech Rep Ser 790 1990. (PubMed id:2110393)

7. Hogerzeil HV, et al. Stability of essential drugs during shipment to the tropics. *BMJ* 1992; 304: 210-14. (PubMed id:1739795)

## **Adverse Effects**

The adverse effects of tetracycline are common to all tetracyclines. Gastrointestinal effects including nausea, vomiting, and diarrhoea are common especially with high doses and most are attributed to irritation of the mucosa. Other effects that have been reported include dry mouth, glossitis and discoloration of the tongue, stomatitis, and dysphagia. Oesophageal ulceration has also been reported, particularly after ingestion of capsules or tablets with insufficient water at bedtime.

Oral candidiasis, vulvovaginitis, and pruritus ani occur, mainly due to overgrowth with *Candida albicans*, and there may be overgrowth of resistant coliform organisms, such as *Pseudomonas* spp. and *Proteus* spp., causing diarrhoea. More seriously, enterocolitis due to superinfection with resistant staphylococci and pseudomembranous colitis due to *Clostridium difficile* have occasionally been reported. It has been suggested that disturbances in the intestinal flora are more common with tetracycline than with better absorbed analogues such as doxycycline.

Renal dysfunction has been reported with tetracyclines, and particularly exacerbation of dysfunction in those with pre-existing renal impairment. Usual therapeutic doses given to patients with renal disease increase the severity of uraemia with increased excretion of nitrogen and losses of sodium, accompanied by acidosis and hyperphosphataemia. These effects are related to the dose and the severity of renal impairment and are probably due to the anti-anabolic effects of the tetracycline. Acute renal failure and nephritis have occurred rarely.

Increases in liver enzyme values have been reported with tetracyclines. In some cases severe and sometimes fatal hepatotoxicity, associated with fatty changes in the liver and pancreatitis, has occurred in pregnant women given tetracycline intravenously for pyelonephritis, and in patients with renal impairment or those given high doses.

Tetracyclines are deposited in deciduous and permanent teeth during their formation, causing discoloration and enamel hypoplasia. They are also deposited in calcifying areas in bone and the nails and interfere with bone growth when given in therapeutic doses to young infants or pregnant women. An increase in intracranial pressure with headache, visual disturbances, and papilloedema has been reported in patients given tetracyclines; the use of tetracyclines in infants has been associated with a bulging fontanelle. If raised intracranial pressure occurs tetracycline treatment should be stopped.

Hypersensitivity to the tetracyclines is much less common than to the beta lactams, but hypersensitivity reactions, including rashes, fixed drug eruptions, exfoliative dermatitis, toxic epidermal necrolysis, drug fever, pericarditis, angioedema, urticaria, and asthma have been reported; anaphylaxis has occurred very rarely. Photosensitivity, which has been reported with most tetracyclines but particularly with demeclocycline and other long-acting analogues, appears to be phototoxic rather than photoallergic in nature. Paraesthesia may be an early sign of impending phototoxicity. Nail discoloration and onycholysis may occur. Abnormal pigmentation of the skin and eye has occurred rarely: permanent discoloration of the cornea has been reported in infants born to mothers given tetracycline in high doses during pregnancy.

Myopia in patients taking tetracyclines may be due to transient hydration of the lens. Local pain and irritation can occur when tetracyclines are given parenterally and thrombophlebitis may follow intravenous injections. A Jarisch-Herxheimer reaction occurs commonly in patients with relapsing fever treated with tetracycline.

Although rare, agranulocytosis, aplastic anaemia, haemolytic anaemia, eosinophilia, neutropenia, and thrombocytopenia have been reported. Tetracyclines may produce hypoprothrombinaemia. They have also been associated with reductions in serum-vitamin B concentrations, including a case of folate deficiency and concomitant megaloblastic anaemia.

The use of out-of-date or deteriorated tetracyclines has been associated with the development of a reversible Fanconi-type syndrome characterised by polyuria and polydipsia with nausea, glycosuria,

aminoaciduria, hypophosphataemia, hypokalaemia, and hyperuricaemia with acidosis and proteinuria; these effects have been attributed to the presence of degradation products, in particular anhydroepitetracycline. Other adverse effects that have occasionally been reported with tetracyclines include increased muscle weakness in patients with myasthenia gravis and provocation of lupus erythematosus.

## **Precautions**

### **Porphyria.**

The tetracyclines are contra-indicated in patients hypersensitive to any of this group of antibacterials, since cross-sensitivity may occur. They should be avoided in patients with systemic lupus erythematosus. In general the tetracyclines, with the exception of doxycycline and perhaps minocycline, are considered to be contra-indicated in renal impairment, particularly if severe: if they must be given, doses should be reduced. Tetracyclines should not be used during pregnancy because of the risk of hepatotoxicity in the mother as well as the effects on the developing fetus. They should also be avoided during breast feeding and in children up to the age of 8, or some authorities say 12, years. Use in pregnancy, potentially during breast feeding, or in childhood, may result in impaired bone growth and permanent discoloration of the child's teeth.

Care should be taken if tetracyclines are given to patients with hepatic impairment and high doses should be avoided. Patients who may be exposed to direct sunlight should be warned of the risk of photosensitivity. Care is advisable in patients with myasthenia gravis, who may be at risk of neuromuscular blockade. Serum monitoring of tetracyclines may be helpful in patients with risk factors receiving parenteral therapy: it has been suggested that serum concentrations of tetracycline should not exceed 15 micrograms/mL. When given by mouth, tetracyclines (notably doxycycline, see Doxycycline Hyclate) should be taken with plenty of fluid while sitting or standing, and well before going to bed, to avoid the risk of oesophageal ulceration.

Tetracycline may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

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## **Breast feeding.**

The American Academy of Pediatrics<sup>1</sup> states that, following use of tetracycline by breast-feeding mothers, there is negligible absorption by the infant and that tetracycline is therefore usually compatible with breast feeding. However, the manufacturers state that adverse effects including permanent tooth discoloration and enamel hypoplasia may occur in breast-fed infants and that breast feeding is contra-indicated during treatment with tetracyclines. 1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776-89. (PubMed id:11533352) Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 28/05/04)

### **Porphyria.**

Tetracyclines are considered to be probably safe in patients with porphyria, although there is conflicting experimental evidence of porphyrinogenicity. Doxycycline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients, and results from animals or in-vitro systems suggest that oxytetracycline might be porphyrinogenic.

## Interactions

The absorption of the tetracyclines is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium, and zinc, and therefore use of tetracyclines with antacids, iron preparations, some foods such as milk and dairy products, or other preparations containing such cations, whether as active ingredients or excipients, may result in subtherapeutic serum concentrations of the antibacterial. Sodium bicarbonate, colestipol, colestyramine, and kaolin-pectin are also reported to reduce tetracycline absorption, but potential reductions due to cimetidine or sucralfate are probably of little clinical significance.

The nephrotoxic effects of tetracyclines may be exacerbated by diuretics, methoxyflurane, or other potentially nephrotoxic drugs. Potentially hepatotoxic drugs should be used with caution in patients receiving tetracyclines. An increased incidence of benign intracranial hypertension has been reported when retinoids and tetracyclines are given together. Tetracyclines have been reported to produce increased concentrations of lithium, digoxin, halofantrine, and theophylline (although these interactions are not strongly established); the effects of oral anticoagulants have also been increased in a few patients. There have been occasional reports of tetracyclines increasing the toxic effects of ergot alkaloids and methotrexate. Tetracyclines may decrease plasma-atovaquone concentrations. Ocular inflammation has occurred following the use of ocular preparations preserved with thiomersal in some patients receiving tetracyclines. Tetracyclines may decrease the effectiveness of oral contraceptives.

**Because of possible antagonism of the action of the penicillins by predominantly bacteriostatic tetracyclines it has been recommended that the two types of drug should not be used together, especially when a rapid bactericidal action is necessary.**

## Antimicrobial Action

The tetracyclines are mainly bacteriostatic, with a broad spectrum of antimicrobial activity including Chlamydiaceae, Mycoplasma spp., Rickettsia spp., spirochaetes, many aerobic and anaerobic Gram-positive and Gram-negative pathogenic bacteria, and some protozoa.

Mechanism of action. Tetracyclines are taken up into sensitive bacterial cells by an active transport process. Once within the cell they bind reversibly to the 30S subunit of the ribosome, preventing the binding of aminoacyl transfer RNA and inhibiting protein synthesis and hence cell growth. Although tetracyclines also inhibit protein synthesis in mammalian cells they are not actively taken up, permitting selective activity against the infecting organism.

Spectrum of activity. The following pathogenic organisms are usually sensitive to tetracyclines: Gram-positive cocci including some strains of Staphylococcus aureus and coagulase-negative staphylococci, and streptococci including Str. pneumoniae, Str. pyogenes (group A), and some viridans streptococci. Enterococci are essentially resistant.

Other sensitive Gram-positive bacteria including strains of Actinomyces israelii, Bacillus anthracis, Erysipelothrix rhusiopathiae, Listeria monocytogenes, and among the anaerobes some Clostridium spp. Nocardia spp. are generally much less susceptible although some are sensitive to minocycline. Propionibacterium acnes is susceptible although the action of the tetracyclines in acne is complex and benefit may be seen even at subinhibitory concentrations.

Gram-negative cocci including Neisseria meningitidis (meningococci) and N. gonorrhoeae (gonococci), although some strains are resistant, and Moraxella catarrhalis (Branhamella catarrhalis). Acinetobacter spp. may be resistant to tetracycline, but most strains are susceptible to doxycycline and minocycline. Other sensitive Gram-negative aerobes including Bordetella pertussis, Brucella spp., Calymmatobacterium granulomatis, **Campylobacter spp.**, Eikenella corrodens, Francisella tularensis, Haemophilus influenzae and some strains of Haemophilus ducreyi, Legionella spp., Pasteurella multocida, Streptobacillus moniliformis, and various members of the Vibrionaceae including Aeromonas hydrophila, Plesiomonas shigelloides, Vibrio cholerae and Vibrio parahaemolyticus. Although many of the Enterobacteriaceae, including

Salmonella, Shigella, and Yersinia spp., are susceptible, resistant strains are common; Proteus and Providencia spp. are not susceptible. Pseudomonas aeruginosa is not susceptible either, although some other species formerly classified as Pseudomonas respond, including Burkholderia mallei, B. pseudomallei, and Stenotrophomonas maltophilia (Xanthomonas maltophilia).

Among the Gram-negative anaerobes Bacteroides fragilis may sometimes be susceptible, although wild strains are often resistant, and Fusobacterium may also be sensitive.

Other organisms usually sensitive to tetracyclines include Helicobacter pylori, Chlamydiaceae, Rickettsia and Coxiella spp., many spirochaetes including Borrelia burgdorferi, Leptospira spp., and Treponema pallidum, atypical mycobacteria such as Mycobacterium marinum, and mycoplasmas including Mycoplasma pneumoniae and Ureaplasma urealyticum. In addition the tetracyclines are active against some protozoa including Plasmodium falciparum and Entamoeba histolytica. Fungi, yeasts, and viruses are generally resistant.

Resistance. Resistance to the tetracyclines is usually plasmid-mediated and transferable. It is often inducible, and appears to be associated with the ability to prevent accumulation of the antibiotic within the bacterial cell, both by decreasing active transport of the drug into the cell and by increasing tetracycline efflux.

Unsurprisingly, given the widespread use of the tetracyclines (including as components of animal feeds, although this is now banned in some countries), resistant strains of the majority of sensitive species have now been reported. Resistance has increased particularly among Enterobacteriaceae such as Escherichia coli, Enterobacter, Salmonella, and Shigella spp., especially in hospital isolates, and multiple resistance is common. Staphylococci are commonly resistant, although doxycycline or minocycline are occasionally effective against tetracycline-resistant strains. Resistance is now also common among group A streptococci, and even more so among group B streptococci; there is also resistance among pneumococci, which often show multiple drug resistance. Emergence of high-level tetracycline-resistant strains of Neisseria gonorrhoeae is common in some areas. Frequent resistance is also seen in clostridia, and in Bacteroides fragilis (among more than 60% of isolates in some countries), while increasing resistance amongst Haemophilus ducreyi has limited the value of tetracyclines in chancroid.

## **Pharmacokinetics**

Most tetracyclines are incompletely absorbed from the gastrointestinal tract, about 60 to 80% of a dose of the drug usually being available. The degree of absorption is diminished by the presence of divalent and trivalent metal ions, with which tetracyclines form stable insoluble complexes, and to a variable degree by milk or food. However, the more lipophilic analogues doxycycline and minocycline are almost completely absorbed (more than 90%), and they are little affected by food. Formulation with phosphate may enhance the absorption of tetracycline.

Administration of tetracycline 500 mg by mouth every 6 hours generally produces steady-state plasma concentrations of 4 to 5 micrograms/mL, whereas with doxycycline a dose of 200 mg is sufficient to produce peak concentrations of about 3 micrograms/mL. Peak plasma concentrations occur about 1 to 3 hours after oral use. Higher concentrations can be achieved after intravenous use; concentrations may be higher in women than in men.

In the circulation, tetracyclines are bound to plasma proteins to varying degrees, but reported values differ considerably ranging from about 20 to 40% for oxytetracycline, 20 to 65% for tetracycline, about 45% for chlortetracycline, 35 to 90% for demeclocycline, 75% for minocycline, and about 80 to 95% for methacycline and for doxycycline.

The tetracyclines are widely distributed throughout the body tissues and fluids. Concentrations in CSF are relatively low, but may be raised if the meninges are inflamed. Small amounts appear in saliva, and in the

fluids of the eye and lung; higher concentrations are achieved with more lipid-soluble analogues such as minocycline and doxycycline. Tetracyclines appear in breast milk, where concentrations may be 60% or more of those in the plasma. They diffuse across the placenta and appear in the fetal circulation in concentrations of about 25 to 75% of those in the maternal blood. Tetracyclines are retained at sites of new bone formation and recent calcification and in developing teeth.

The tetracyclines have been classified in terms of their duration of action in the body, although the divisions appear to overlap somewhat. Of the 'short-acting' derivatives, chlortetracycline has a reported half-life of about 6 hours, oxytetracycline 9 hours, and tetracycline 8 hours, although reported values for the latter two range from about 6 to 12 hours. The 'intermediate-acting' tetracyclines, demeclocycline and methacycline, have reported half-lives of about 12 and 14 hours respectively, although various sources cite values of 7 to 17 hours, and the 'long-acting' minocycline and doxycycline have half-lives of about 16 and 18 hours, with reported values anywhere between 11 to 26 and 12 to 24 hours respectively.

The tetracyclines are excreted in the urine and in the faeces. Renal clearance is by glomerular filtration. Up to 60% of an intravenous dose of tetracycline, and up to 55% of a dose by mouth, is eliminated unchanged in the urine; tetracycline concentrations in the urine of up to 300 micrograms/mL may be reached 2 hours after a usual dose is taken and be maintained for up to 12 hours. Usually about 40 to 70% of a dose is excreted in the urine, but for chlortetracycline, doxycycline, and minocycline, rather less is eliminated by this route since chlortetracycline and minocycline undergo metabolism, and doxycycline is excreted mainly in the faeces. Urinary excretion is increased if urine is alkalinised.

The tetracyclines are excreted in the bile, where concentrations 5 to 25 times those in plasma can occur. Since there is some enterohepatic reabsorption complete elimination is slow. Considerable quantities occur in the faeces after administration by mouth and lesser amounts after administration by injection.

## Uses and Administration

Administration in hepatic impairment.  
Malaria.  
Mouth ulceration.  
Peptic ulcer disease.  
Rheumatic disorders.  
Skin disorders.  
Pemphigus and pemphigoid.  
Rosacea.

The tetracyclines are bacteriostatic antibiotics with a wide spectrum of activity and have been used in the treatment of a large number of infections caused by susceptible organisms. With the emergence of bacterial resistance and the development of other antibacterials their use has become more restricted, but they remain drugs of choice in rickettsial infections, including ehrlichiosis, Q fever, spotted fevers, and typhus; trench fever; chlamydial infections, including psittacosis, lymphogranuloma venereum, trachoma, non-gonococcal urethritis, and conjunctivitis, and also pharyngitis, sinusitis, or pneumonia due to *Chlamydia pneumoniae*; and mycoplasmal infections, especially pneumonia caused by *Mycoplasma pneumoniae*. They are widely used as part of regimens for pelvic inflammatory disease. A tetracycline is often used in the treatment of cholera, in conjunction with fluid and electrolyte replacement, and is usually the treatment of choice in relapsing fever and in the early stages of Lyme disease. They are also used in the oral treatment of acne (Tetracycline Phosphate Complex) and rosacea.

Tetracyclines may be of benefit in the treatment of melioidosis. They may be used for mouth infections, especially in destructive forms of periodontal disease. Tetracyclines are used, often with streptomycin or

rifampicin, in the treatment of brucellosis, and may be given with streptomycin in plague, and as an alternative to streptomycin in the treatment of tularaemia. Tetracyclines are used as an alternative to other drugs in the treatment of actinomycosis, infected animal bites, anthrax, bronchitis, gastro-enteritis (due to *Campylobacter* or *Yersinia enterocolitica*), granuloma inguinale, leptospirosis, and syphilis. Opinions differ as to their value in listeriosis. There are now relatively few areas where tetracycline-resistant gonococci are uncommon, which limits the value of tetracyclines in gonorrhoea, but they are often given with antigonorrhoeal therapy to treat concomitant chlamydial infections, and they retain some value in the prophylaxis and treatment of neonatal gonococcal conjunctivitis by topical application. For details of these infections and their treatment, see under Choice of Antibacterial, Antibacterials.

Tetracyclines have antiprotozoal actions and tetracycline or doxycycline may be given with quinine in the management of falciparum malaria resistant to chloroquine (Tetracycline Phosphate Complex).

Tetracyclines are the usual treatment for balantidiasis (Antiprotozoals) and they have been used with an amoebicide in the treatment of severe amoebic dysentery and in *Dientamoeba fragilis* infections (Antiprotozoals).

Tetracycline has been used in the management of malabsorption syndromes such as tropical sprue. Tetracycline has been instilled as a sclerosant solution for pleurodesis and in the management of malignant effusions (Antineoplastics).

**Administration and dosage.** In the treatment of systemic infections the tetracyclines are usually given by mouth. They should be taken with plenty of fluid while sitting or standing, and well before going to bed, to avoid the risk of oesophageal ulceration. In severe acute infections they may be given by slow intravenous infusion or, rarely, by intramuscular injection; parenteral therapy should be substituted by oral administration as soon as practicable.

Doses of tetracycline base and tetracycline hydrochloride are expressed in terms of tetracycline hydrochloride. Tetracycline (anhydrous) 0.92 g is approximately equivalent to 1 g of tetracycline hydrochloride. The usual adult dosage of tetracycline hydrochloride is 250 or 500 mg every 6 hours by mouth, preferably 1 hour before or 2 hours after meals. Higher doses, up to 4 g daily have occasionally been given in severe infection, but increase the risk of adverse effects. Modified-release formulations are available in some countries.

In severe infections, tetracycline hydrochloride has been given by slow intravenous infusion every 12 hours as a solution containing not more than 0.5% in a usual total dose of 0.5 to 1 g daily, although up to 2 g daily has been given. If the intramuscular route is to be used, tetracycline hydrochloride has been given in a dosage of 250 mg once daily, or 300 mg daily in divided doses. As intramuscular injections are painful, procaine hydrochloride is usually included in the solution.

In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential. Tetracycline hydrochloride has been given to older children (over 8 years) in doses of 25 to 50 mg/kg daily by mouth in divided doses.

Care is required if tetracyclines are given to the elderly. They should be avoided if possible in renal impairment (with the exception of doxycycline and minocycline) and doses reduced if they must be used. For dosage recommendations in patients with hepatic impairment, see Tetracycline Phosphate Complex. Other routes. Although topical application carries the risk of sensitisation and may contribute to the development of resistance, tetracycline hydrochloride has been used as a 3% ointment; a 0.2% solution has been used in acne but systemic treatment appears to produce better results. A 1% eye ointment or eye drops have been used in the treatment of ocular infections due to sensitive organisms. For the treatment of pleural effusions, 500 mg of tetracycline hydrochloride has been dissolved in 30 to 50 mL of sodium chloride 0.9% and instilled into the pleural space. For periodontal disease, fibres that release tetracycline have been inserted into the periodontal pocket. Reviews. 1. Chopra I, et al. Tetracyclines, molecular and clinical aspects. *J Antimicrob Chemother* 1992; 29: 245-77. (PubMed id:1592696)

### **Administration in hepatic impairment.**

The manufacturers state that the dosage of tetracycline should not exceed 1 g daily in patients with known liver disease.

### **Malaria.**

Tetracyclines have been used with quinine to treat malaria (Antimalarials).<sup>1</sup> They are active against both blood and tissue forms of the parasite, and high cure rates have been obtained with such combinations. The action of tetracyclines is relatively slow and they should never be used alone to treat malaria.

A usual oral regimen is a 3-day course of quinine given concurrently with 7 to 10 days of the tetracycline. The dose of tetracycline hydrochloride has varied; doses of 1 to 2 g daily have been given for 7 days or 1 g daily for 7 to 10 days. The total daily dose should be divided, and that usually recommended is 250 mg four times daily, although 500 mg twice daily may be more practical in the field. If the patient is too ill for oral medication quinine should be given parenterally until oral therapy can be begun; tetracycline should not be used parenterally. Although tetracycline therapy is normally contra-indicated in pregnant women and children, it may have to be given if the risk of withholding the drug is judged to outweigh the risk to developing teeth and bones. The dose of doxycycline given by mouth following treatment with quinine is 200 mg daily for at least 7 days.

Tetracyclines are not considered suitable for extended prophylactic use, although doxycycline 100 mg daily has been used for short-term prophylaxis in areas of high risk where other drugs are likely to be ineffective.

1. WHO. WHO model prescribing information: drugs used in parasitic diseases. 2nd ed. Geneva: WHO, 1995.

### **Mouth ulceration.**

Tetracyclines may be used as mouthwashes in recurrent aphthous stomatitis (Gastrointestinal Drugs) and reportedly reduce ulcer pain and duration,<sup>1</sup> but their potential for adverse effects if swallowed must be borne in mind, and their acidity can damage tooth enamel if poorly formulated. Topical application of a tetracycline has been tried for oral ulceration associated with Behçet's syndrome (Corticosteroids).<sup>1</sup>

Henricsson V, Axéll T. Treatment of recurrent aphthous ulcers with Aureomycin mouth rinse or Zendium dentifrice. *Acta Odontol Scand* 1985; 43: 47-52. (PubMed id:3925707)

### **Peptic ulcer disease.**

**Tetracycline has been used as part of triple therapy to eradicate Helicobacter pylori in patients with peptic ulcer disease (Gastrointestinal Drugs).**

**The usual dose of tetracycline in these regimens has been 500 mg four times daily for 2 weeks.**

### **Rheumatic disorders.**

Tetracyclines, usually minocycline, are among the wide range of drugs tried in rheumatoid arthritis (Analgesics Anti-inflammatory Drugs and Antipyretics). Studies<sup>1,2</sup> indicate that minocycline can produce modest beneficial effects in patients with advanced rheumatoid arthritis, but the clinical significance of these improvements has been questioned.<sup>3</sup> Greater symptomatic improvements have been obtained with minocycline when it is used in patients with early rheumatoid arthritis;<sup>4,5</sup> continued treatment with minocycline may also reduce the need for disease-modifying antirheumatic drugs.<sup>6</sup> Its mechanism of action, whether antibacterial or anti-inflammatory, remains to be determined.<sup>7</sup> There has been speculation over the role of infection as a cause of rheumatoid arthritis.<sup>3,8</sup>

The role of antibacterials is also uncertain in reactive arthritis (Antibacterials), although long-term treatment with a tetracycline in addition to an NSAID has been reported to shorten the duration of reactive arthritis resulting from *Chlamydia trachomatis* infection.<sup>9</sup> 1. Kloppenburg M, et al. Minocycline in active rheumatoid arthritis. *Arthritis Rheum* 1994; 37: 629-36. (PubMed id:8185689)

2. Tilley BC, et al. Minocycline in rheumatoid arthritis: a 48-week, double-blind, placebo-controlled trial. *Ann Intern Med* 1995; 122: 81-9. (PubMed id:7993000)
3. McKendry RJR. Is rheumatoid arthritis caused by an infection? *Lancet* 1995; 345: 1319-20. (PubMed id:7752751)
4. O'Dell JR, et al. Treatment of early rheumatoid arthritis with minocycline or placebo: results of a randomized double-blind, placebo-controlled trial. *Arthritis Rheum* 1997; 40: 842-8. (PubMed id:9153544)
5. O'Dell JR, et al. Treatment of early seropositive rheumatoid arthritis: a two-year, double-blind comparison of minocycline and hydroxychloroquine. *Arthritis Rheum* 2001; 44: 2235-41. (PubMed id:11665963)
6. O'Dell JR, et al. Treatment of early seropositive rheumatoid arthritis with minocycline: four-year follow-up of a double-blind, placebo-controlled trial. *Arthritis Rheum* 1999; 42: 1691-5. (PubMed id:10446869)
7. Paulus HE. Minocycline treatment of rheumatoid arthritis. *Ann Intern Med* 1995; 122: 147-8. (PubMed id:7992990)
8. O'Dell JR. Is there a role for antibiotics in the treatment of patients with rheumatoid arthritis? *Drugs* 1999; 57: 279-82. (PubMed id:10193682)
9. Laihio A. Reactive arthritis: consider combination treatment. *BMJ* 1994; 308: 1302-3. (PubMed id:8205036)

## Skin disorders.

### Acne.

Tetracyclines may be used topically or orally in the treatment of acne (Dermatological Drugs and Sunscreens). In acne, antibacterials appear to act by suppressing the growth of *Propionibacterium* acnes, but also by suppressing inflammation. Topical tetracycline is used for mild inflammatory acne and as an adjunct to systemic treatment in more severe forms. Tetracyclines, given orally, are the drugs of choice for moderate acne and may be considered, in high doses, for severe acne. Licensed doses in the UK are: doxycycline 50 mg daily; minocycline 100 mg daily; oxytetracycline 250 to 500 mg daily; and tetracycline 1 g daily. Higher doses for doxycycline of 100 mg daily and for oxytetracycline of 1 g daily are advocated in the British National Formulary. Treatment should be changed to another antibacterial if there has been no improvement in the first 3 months. Maximum improvement is said to occur after 3 to 6 months, but treatment may need to continue for 2 or more years.

Minocycline has been reported to have superior antibacterial activity against *P. acnes* and a reduced incidence of resistance,<sup>1</sup> and has also been more effective than erythromycin against oxytetracycline-resistant acne.<sup>2</sup> However, it can cause skin pigmentation and may be associated rarely with immunologically mediated reactions<sup>3</sup> and some dermatologists do not favour its use. Although the usual dose of minocycline is 100 mg daily in one or two divided doses some patients may need up to 200 mg daily.<sup>4</sup>

1. Eady EA, et al. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. *Br J Dermatol* 1990; 122: 233-44. (PubMed id:2138493)

2. Knaggs HE, et al. The role of oral minocycline and erythromycin in tetracycline therapy-resistant acne--a retrospective study and a review. *J Dermatol Treat* 1993; 4: 53-6.
3. Ferner RE, Moss C. Minocycline for acne. *BMJ* 1996; 312: 138. (PubMed id:8563527)
4. Goulden V, et al. Safety of long-term high-dose minocycline in the treatment of acne. *Br J Dermatol* 1996; 134: 693-5. (PubMed id:8733373)

### Pemphigus and pemphigoid.

Corticosteroids are generally given to control the blistering in pemphigus and pemphigoid (Dermatological Drugs and Sunscreens), although there have been reports<sup>1-3</sup> suggesting that a tetracycline (often minocycline) may be of value in controlling the lesions associated with various types of pemphigus and pemphigoid.

1. Sawai T, et al. Pemphigus vegetans with oesophageal involvement: successful treatment with minocycline and nicotinamide. *Br J Dermatol* 1995; 132: 668-70. (PubMed id:7748766)

2. Poskitt L, Wojnarowska F. Minimizing cicatricial pemphigoid orodynia with minocycline. *Br J Dermatol* 1995; 132: 784-9. (PubMed id:7772486)
3. Kolbach DN, et al. Bullous pemphigoid successfully controlled by tetracycline and nicotinamide. *Br J Dermatol* 1995; 133: 88-90. (PubMed id:7669647)

### Rosacea.

Tetracycline is commonly used in the treatment of rosacea (Dermatological Drugs and Sunscreens). Long-term treatment is usually necessary. Tetracycline and doxycycline have also been shown to improve ocular manifestations of rosacea.1 1. Frucht-Pery J, et al. Efficacy of doxycycline and tetracycline in ocular rosacea. *Am J Ophthalmol* 1993; 116: 88-92. (PubMed id:8328549)

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