

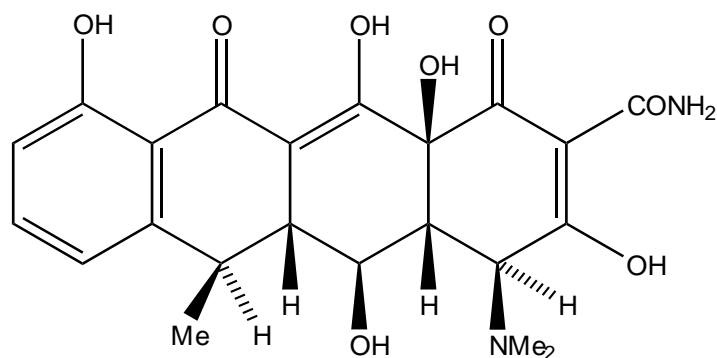
APO-DOXYCYCLINE TABLETS

NAME OF THE MEDICINE

Doxycycline monohydrate

Chemical Name: 4*S*, 4*aR*,5*S*,5*aR*,6*R*,12*aS*)-4-dimethylamino-1,4,4*a*,5,5*a*,6,11,12*a*-octahydro-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide monohydrate

Structural Formula:



Molecular Weight: 462.5

CAS number: 17086-28-1

DESCRIPTION

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. The chemical designation of this light-yellow crystalline powder is 6-deoxy-5-oxytetracycline. Doxycycline has a high lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. It will not degrade into an epianhydro form.

Doxycycline tablets are intended for oral administration and each tablet contains doxycycline 50 mg or 100 mg (as monohydrate). In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, hydrogenated castor oil, povidone, colloidal silicon dioxide and magnesium stearate.

PHARMACOLOGY

Doxycycline is a broad spectrum antibiotic synthetically derived from oxytetracycline

Pharmacological Actions

Microbiology

Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect through inhibition of protein synthesis. It is active against a wide range of Gram-positive and Gram-negative organisms.

Susceptibility Testing

The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross resistance among them is common. Micro-organisms may be considered susceptible if the MIC (minimum inhibitory concentration) is less than 1.0 µg/mL and intermediate if the MIC is 1.0 to 5.0 µg/mL.

Disc 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 disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.

A report of “susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “intermediate” indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to the alternative, clinically feasible drugs, the tests should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation. A report of “resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reached concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Tetracyclines are readily absorbed though to a varying extent. They are concentrated by the liver in the bile, and excreted in the urine and faeces at high concentrations and in a biologically active form.

Absorption

Doxycycline is virtually completely absorbed after oral administration. Its absorption is not significantly affected by the presence of food or milk.

Distribution

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 µg/ mL of doxycycline at 2 hours decreasing to 1.45 µg/ mL at 24 hours. There is limited diffusion of doxycycline into cerebrospinal fluid after oral administration.

Metabolism

The metabolism of doxycycline in the human body has not been investigated. *In vitro* serum protein binding of doxycycline varies from 23 to 93%.

Excretion

Excretion of doxycycline by the kidney is about 40% in 72 hours in individuals with normal renal function (creatinine clearance above 75 mL/minute). This percentage excretion may fall as low as 1 to 5% in 72 hours in individuals with severe renal insufficiency creatinine clearance below 10 mL/minute). Studies have shown no significant difference in serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function.

The fraction of drug that is not eliminated with urine is mainly excreted in the faeces. More than 90% of an oral dose of doxycycline is eliminated from the body within 72 hours of drug administration.

Haemodialysis does not alter serum half-life.

INDICATIONS

Infections caused by the following microorganisms:

- *Mycoplasma pneumoniae*: primary atypical pneumonia
- *Rickettsiae*: Queensland tick typhus, epidemic typhus fever, Q fever, murine endemic typhus fever, Australo-Pacific endemic scrub typhus);
- *Chlamydia psittaci* (psittacosis);
- *Chlamydia trachomatis* (lymphogranuloma venereum, trachoma, inclusion conjunctivitis).

(Doxycycline 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 doxycycline, or in combination with topical agents.)

- *Calymmatobacterium* (Donovania) *granulomatis* (granuloma inguinale).

And the following Gram-negative micro-organisms:

- *Vibrio species* (cholera);
- *Brucella species* (brucellosis (in conjunction with streptomycin));
- *Yersinia pestis* (plague);
- *Francisella tularensis* (tularemia);
- *Bartonella bacilliformis* (bartonellosis);
- *Bacteroides species*

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

- *Treponema pallidum* (syphilis);
- *Treponema pertenue* (yaws);
- *Neisseria gonorrhoea* (see **DOSAGE AND ADMINISTRATION**)

Note:

Doxycycline is not the drug of choice in the treatment of any type of staphylococcal infection or infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Streptococcus faecalis*, or any type of enteric bacteria because many strains of these organisms have been shown to be resistant to doxycycline. Doxycycline should not be used in these infections unless the organism has been shown to be sensitive. For upper respiratory tract infections due to group A beta-haemolytic streptococci (including prophylaxis of rheumatic fever) penicillin is the usual drug of choice.

In acute intestinal amoebiasis doxycycline may be a useful adjunct to amoebicides.

In severe acne doxycycline may be a useful adjunctive therapy.

Doxycycline is indicated, in adults and children older than 10 years, as chemoprophylaxis for malaria caused by *Plasmodium falciparum* and, in combination with other antimalarial agents, against malaria caused by *Plasmodium vivax*. Doxycycline is only able to suppress malaria caused by *P. vivax*. As there are relatively few locations where *P. vivax* does not co-exist to some extent with *P. falciparum*, it is recommended that doxycycline should be used routinely with other agents, for example chloroquine.

CONTRAINDICATIONS

- Hypersensitivity to any of the tetracyclines or any of the excipients of doxycycline tablets
- Use in pregnancy (16 weeks post conception) and use in lactation (see **PRECAUTIONS**)
- Rare cases of benign intracranial hypertension have been reported after tetracyclines and oral retinoids such as isotretinoin or etretinate and Vitamin A. Concomitant treatment is therefore contraindicated (see **PRECAUTIONS** and **ADVERSE EFFECTS**).

PRECAUTIONS

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Intracranial Hypertension

Intracranial hypertension (IH) has been associated with the use of tetracyclines including doxycycline (see **CONTRAINDICATIONS** and **ADVERSE EFFECTS**). The use of tetracyclines in infants, even in the usual therapeutic doses, may cause increased intracranial pressure and bulging of the fontanelles. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Clinical manifestations include headache, blurred vision, diplopia and vision loss. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Discontinuation of therapy typically results in prompt return of the pressure to normal. However, since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilise

Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients likely 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.

Use in Renal Impairment

The anti-anabolic action of the tetracyclines may cause an increase in serum urea. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Use in Hepatic Impairment

Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Gastrointestinal Disease

History of colitis: Antibiotics should be prescribed with care for individuals with a history of gastrointestinal disease, especially ulcerative colitis, regional enteritis or antibiotic associated colitis.

Pseudomembranous colitis: *Clostridium difficile* associated diarrhoea (CDAD) and antibiotic associated pseudomembranous colitis have been reported with nearly all antibiotics including doxycycline, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile* and *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

Concomitant Diseases

In venereal disease when coexistent syphilis is suspected, proper diagnostic measures including a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least four months.

Long Term Use

In long term therapy, periodic laboratory evaluation of organ systems, including haemopoietic, renal and hepatic studies should be performed.

If doxycycline is used to treat infections due to group A beta-haemolytic streptococci, treatment should continue for at least 10 days.

Oesophagitis

Rarely, oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline tablets. Most of these patients took medication immediately before going to bed. Patients should be instructed to take doxycycline with plenty of water (at least 100mL), remain upright and not take their treatment before going to bed. Withdrawal of doxycycline and investigation of oesophageal disease should be considered if symptoms such as dyspepsia or retrosternal pain occur. Caution is required in the treatment of patients with known oesophageal reflux disorders.

To reduce the possibility of gastric irritation it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Use in Pregnancy (Category D)

(See **CONTRAINDICATIONS**).

Tetracyclines are safe for use during the first 18 weeks of pregnancy, after which they cause discolouration of the baby's teeth.

During the period of mineralisation of a child's teeth (the last half 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 latter half of pregnancy.

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk. A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and fifty six (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (i.e., in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases.

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.

Results in animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Large doses of tetracyclines have caused acute fatty necrosis of the liver in pregnant women, especially those with pyelonephritis. Large doses of the medicine should not be used in pregnant women, or those likely to become pregnant.

Use in Lactation

(See **PRECAUTIONS** and **Paediatric Use**)

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown. Because of the potential for serious adverse reactions in breastfed infants from doxycycline, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Use

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines also interfere with tooth development (see above, **Use in Pregnancy**). The use of the drugs of the tetracycline class, including doxycycline, during tooth development (latter half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This 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. Therefore doxycycline should not be used in children younger than 8 years of age unless other drugs are not likely to be effective or are contraindicated.

Effects on Laboratory Test

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

INTERACTIONS WITH OTHER MEDICINES**Anticoagulants**

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

Antacids

Antacids containing aluminium, calcium or magnesium, or other drugs containing these cations, bismuth salts and preparations containing iron impair absorption and should not be given to patients taking doxycycline.

Antibiotics

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

Oral Contraceptives

There are anecdotal reports that concurrent use of tetracyclines may render oral contraceptives less effective.

Methoxyflurane

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity.

Other

Plasma levels of doxycycline are reduced by the ingestion of alcohol or the administration of barbiturates, anticonvulsants (phenytoin, carbamazepine), disodium hydrogen edetate, sodium bicarbonate, sodium lactate, acetazolamide and ethoxzolamide.

ADVERSE EFFECTS

Doxycycline is generally well tolerated.

Due to its virtually complete absorption, side effects of the lower bowel, particularly diarrhoea, have been infrequent. The following adverse effects have been observed in patients receiving doxycycline:

More Common Effects

Dermatological

Photosensitive skin reactions (**see PRECAUTIONS**), erythematous rash, maculopapular rash, morbilliform rash, pustular rash, urticaria, photo-onycholysis and discolouration of the nails.

Gastrointestinal

Nausea, anorexia, vomiting, dysphagia, diarrhoea, oesophagitis, oesophageal ulceration, abdominal pain, glossitis, black hairy tongue.

Hypersensitivity

Urticaria, exacerbation of systemic lupus erythematosus.

Hepatic

Cholestatic hepatitis, fatty liver degeneration.

Renal

Dose related increase in serum urea (**see PRECAUTIONS**).

Musculoskeletal

Tooth discolouration, enamel hypoplasia.

Other

Bulging fontanelles have been reported in young infants following full therapeutic dosage. The sign disappeared rapidly when the drug was discontinued.

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

Less Common Effects

Gastrointestinal

Enterocolitis (**see PRECAUTIONS**), inflammatory lesions (with monilial overgrowth) in the anogenital region, dyspepsia and pseudomembranous colitis (**see PRECAUTIONS**), *C. difficile* diarrhoea, hepatotoxicity, hepatitis. Abnormal hepatic function has been reported rarely (<1/1000), pancreatitis

-Dermatological

Exfoliative dermatitis, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN).

Musculoskeletal

Arthralgia, myalgia.

Genitourinary

Acute renal failure.

Hypersensitivity

Angioneurotic oedema, anaphylaxis, anaphylactic shock, anaphylactic reaction, anaphylactoid purpura, pericarditis, serum sickness, hypotension, dyspnoea, peripheral oedema, tachycardia, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS).

Haematological and Reticuloendothelial

Phlebitis associated with intravenous administration; leucopenia; thrombocytopenic purpura; increase in

prothrombin time; haemolytic anaemia, eosinophilia, neutropenia.

Nervous System

Flushing, malaise; headache, confusion; taste loss; stupor; hypoaesthesia; paraesthesia; somnolence; benign intracranial hypertension in adults, increased intracranial pressure in infants. In relation to benign intracranial hypertension, symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.

Ocular

Conjunctivitis, periorbital oedema.

Hearing / Vestibular

Tinnitus

Psychiatric

Depression, anxiety, hallucination.

Respiratory

Bronchospasm.

Hepatic

Hepatotoxicity

DOSAGE AND ADMINISTRATION

Administration of adequate amounts of fluid with the tablets is recommended to reduce the risk of oesophageal irritation and ulceration. Morning (rather than late night) dosing may be preferable. As the recumbent posture may delay oesophageal transit of the tablets, the patient should not lie down for some time after taking the tablets. To reduce the possibility of gastric irritation, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk. Antacids containing aluminium, calcium or magnesium and preparations containing iron impair absorption and should not be given to patients taking doxycycline.

The usual dosage and frequency of administration of doxycycline differs from that of other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued at least 24 to 48 hours after symptoms and fever have subsided.

Tetracyclines are not the drugs of choice for the treatment of streptococcal infections (see **INDICATIONS**). However, when used, therapy should be continued for ten days.

Adults and Children Over 8 Years (and \geq 50 kg in weight)

The usual dose of doxycycline is 200 mg on the first day of treatment (administered as 100 mg every twelve hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every twelve hours. A 50 mg dose can be delivered using half of one 100 mg tablet or one whole 50 mg tablet. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every twelve hours is recommended.

Acute Uncomplicated Gonococcal Infections

100 mg twice daily for five to seven days.

Resistance to tetracyclines is not uncommon amongst gonococci. The use of tetracyclines in the treatment of gonorrhoea should, therefore, be accompanied by monitoring of efficacy.

Primary and Secondary Syphilis

300 mg/day in divided doses for at least ten days.

Louse-borne typhus

This has been successfully treated with a single oral dose of 100 mg or 200 mg according to severity.

Prevention of Scrub Typhus

200 mg as a single dose.

Children Over 8 Years (and < 50 KG without Skeletal Growth)

The adult dose of 100 mg should be calculated on a weight basis of 2 mg/kg (see **PRECAUTIONS, Paediatric Use**).

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Severe Acne

Some efficacy has been demonstrated in some individuals at a dose of 50 mg/day over a period of 12 weeks. No data showing efficacy beyond 12 weeks have been submitted.

Malaria Chemoprophylaxis

100 mg once a day; commencing two days prior to entering malarious areas, while in the malarious area and for four weeks after leaving the malarious area. A maximum of 100 mg daily for eight weeks is recommended, as safety after eight weeks has not been clearly established (see **PHARMACOLOGY**, and **INDICATIONS** about combination with other antimalarial agents for prophylaxis against *P. vivax*).

OVERDOSAGE

Symptoms

Tetracyclines, including doxycycline, generally have low toxicity. Severe toxicity following acute overdose is unlikely, with nausea and vomiting being the most common effects after ingestion of therapeutic and overdose amounts.

Treatment

Treatment may include immediate discontinuation of medication, dilution with water or milk and general supportive care. Antacids may be useful in managing gastric irritation. In most cases, gastrointestinal decontamination is not required. Plasma levels are not clinically useful and specific laboratory monitoring is not needed unless otherwise indicated.

In case of an oral overdose with doxycycline, gastric lavage should be considered to remove unabsorbed portions of the substance. Remaining residues of doxycycline should be minimised by administering antacids or calcium or magnesium salt in order to produce non-absorbable chelates.

Doxycycline is not sufficiently dialysable. Thus, haemodialysis or peritoneal dialysis is not very effective. In massive overdose, there is a risk of liver damage sometimes accompanied by pancreatitis.

In massive overdose, there is a risk of liver damage sometimes accompanied by pancreatitis

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

APO-Doxycycline Tablets are intended for oral administration.

Each tablet contains 50 mg or 100 mg of doxycycline (as monohydrate), as the active ingredient.

50 mg Tablets

Dull yellow, round, biconvex tablets.
Blister pack (PP/Al) of 25 tablets.
(AUST R 78597).

100 mg Tablets

Dull yellow, round, biplane tablets with a single sided score notch.
Blister packs (PP/Al) of 7 and 21 tablets.
(AUST R 78598).

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty. Ltd.
16 Giffnock Avenue
Macquarie Park NSW 2113

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POISON SCHEDULE OF THE MEDICINE

S4: Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

25 May 2001

DATE OF MOST RECENT AMENDMENT

9 January 2017