

69-1940-00-3

VIBRAMYCIN[®]
hyclate
doxycycline hyclate for injection

INTRAVENOUS
FOR INTRAVENOUS USE ONLY

DESCRIPTION

Vibramycin (doxycycline hyclate for injection) Intravenous is an antibacterial drug synthetically derived from oxytetracycline, and is available as Vibramycin Hyclate (doxycycline hydrochloride hemiethanolate hemihydrate). The chemical designation of this light-yellow crystalline powder is alpha-6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum.

ACTIONS

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

The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common. Microorganisms may be considered susceptible to doxycycline (likely to respond to doxycycline therapy) if the minimum inhibitory concentration (M.I.C.) is not more than 4.0 mcg/mL. Microorganisms may be considered intermediate (harboring partial resistance) if the M.I.C. is 4.0 to 12.5 mcg/mL and resistant (not likely to respond to therapy) if the M.I.C. is greater than 12.5 mcg/mL.

Susceptibility plate testing: If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg doxycycline disc should give a zone of at least 16 mm when tested against a doxycycline-susceptible bacterial strain. A tetracycline disc may be used to determine microbial susceptibility. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg tetracycline disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form.

Following a single 100 mg dose administered in a concentration of 0.4 mg/mL in a one-hour infusion, normal adult volunteers average a peak of 2.5 mcg/mL, while 200 mg of a concentration of 0.4 mg/mL administered over two hours averaged a peak of 3.6 mcg/mL.

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

Hemodialysis does not alter this serum half-life of doxycycline.

INDICATIONS

Doxycycline is indicated in infections caused by the following microorganisms:

- Rickettsiae (Rocky Mountain spotted fever, typhus fever, and the typhus group, Q fever, rickettsialpox and tick fevers).
- Mycoplasma pneumoniae* (PPLO, Eaton Agent).
- Agents of psittacosis and ornithosis.
- Agents of lymphogranuloma venereum and granuloma inguinale.
- The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:

- Haemophilus ducreyi* (chancroid),
- Pasteurella pestis* and *Pasteurella tularensis*,
- Bartonella bacilliformis*,
- Bacteroides* species,
- Vibrio comma* and *Vibrio fetus*,
- Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms when bacteriologic 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).

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Streptococcus species:

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines

should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

Diplococcus pneumoniae,
Staphylococcus aureus, respiratory skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

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

Neisseria gonorrhoeae and *N. meningitidis*,
Treponema pallidum and *Treponema pertenue* (syphilis and yaws),
Listeria monocytogenes,
Clostridium species,
Fusobacterium fusiforme (Vincent's infection),
Actinomyces species.

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

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

CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-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, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), 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 tetracyclines. 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.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Usage in Pregnancy

(See above WARNINGS about use during tooth development.)

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal 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.

Usage in Children

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

(See above WARNINGS about use during tooth development.)

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 prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

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

PRECAUTIONS

As with other antibacterial drugs, use of Vibramycin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, Vibramycin should be discontinued and appropriate therapy instituted.

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including Vibramycin. Clinical manifestations of IH include headache, blurred vision, diplopia, vision loss, and papilledema. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin and Vibramycin should be avoided because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, it is possible that permanent visual loss can occur. If visual symptoms develop during treatment, prompt

ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

In venereal diseases when coexistent syphilis is suspected, a dark field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

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 hematopoietic, renal, and hepatic studies should be performed.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

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

ADVERSE REACTIONS

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.

Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See WARNINGS.)

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See WARNINGS.)

Immune: Hypersensitivity reactions including urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, and drug rash with eosinophilia and systemic symptoms (DRESS).

Bulging fontanel in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported.

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

DOSAGE AND ADMINISTRATION

Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF VIBRAMYCIN I.V. (100-200 MG/DAY) DIFFERS FROM THAT OF THE OTHER TETRACYCLINES (1-2 G/DAY). EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

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

Adults: The usual dosage of Vibramycin I.V. is 200 mg on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg depending upon the severity of infection, with 200 mg administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

For children above eight years of age: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg/lb of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See WARNINGS Section for Usage in Children.)

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 1 mg/lb (2.2 mg/kg) of body weight, twice a day in children weighing less than 100 lb (45 kg). Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

General: The duration of infusion may vary with the dose (100 to 200 mg per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg of a 0.5 mg/mL solution is one hour. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly or subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

PREPARATION OF SOLUTION

To prepare a solution containing 10 mg/mL, the contents of the vial should be reconstituted with 10 mL (for the 100 mg/vial container) or 20 mL (for the 200 mg/vial container) of Sterile Water for Injection or any of the ten intravenous infusion solutions listed below. Each 100 mg of Vibramycin (i.e., withdraw entire solution from the 100 mg vial) is further diluted with 100 mL to 1000 mL of the intravenous solutions listed below. Each 200 mg of Vibramycin (i.e., withdraw entire solution from the 200 mg vial) is further diluted with 200 mL to 2000 mL of the following intravenous solutions:

1. Sodium Chloride Injection, USP
2. 5% Dextrose Injection, USP
3. Ringer's Injection, USP
4. Invert Sugar, 10% in Water
5. Lactated Ringer's Injection, USP
6. Dextrose 5% in Lactated Ringer's
7. Normosol-M[®] in D5-W (Abbott)
8. Normosol-R[®] in D5-W (Abbott)
9. Plasma-Lyte[®] 56 in 5% Dextrose (Travenol)
10. Plasma-Lyte[®] 148 in 5% Dextrose (Travenol)

This will result in desired concentrations of 0.1 to 1.0 mg/mL. Concentrations lower than 0.1 mg/mL or higher than 1.0 mg/mL are not recommended.

Stability

Vibramycin IV is stable for 48 hours in solution when diluted with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to concentrations between 1.0 mg/mL and 0.1 mg/mL and stored at 25°C. Vibramycin IV in these solutions is stable under fluorescent light for 48 hours, but must be protected from direct sunlight during storage and infusion. Reconstituted solutions (1.0 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Vibramycin IV, when diluted with Ringer's Injection, USP, or Invert Sugar, 10% in Water, or Normosol-M[®] in D5-W (Abbott), or Normosol-R[®] in D5-W (Abbott), or Plasma-Lyte[®] 56 in 5% Dextrose (Travenol), or Plasma-Lyte[®] 148 in 5% Dextrose (Travenol) to a concentration between 1.0 mg/mL and 0.1 mg/mL, must be completely infused within 12 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Reconstituted solutions (1.0 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

When diluted with Lactated Ringer's Injection, USP, or Dextrose 5% in Lactated Ringer's, infusion of the solution (ca. 1.0 mg/mL) or lower concentrations (not less than

0.1 mg/mL) must be completed within six hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.

Solutions of Vibramycin (doxycycline hyclate for injection) at a concentration of 10 mg/mL in Sterile Water for Injection, when frozen immediately after reconstitution are stable for 8 weeks when stored at -20°C . If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

HOW SUPPLIED

Vibramycin (doxycycline hyclate for injection) Intravenous is available as a sterile powder in a vial containing doxycycline hyclate equivalent to 100 mg of doxycycline with 480 mg of ascorbic acid; packages of 5 (0049-0960-77), and in individually packaged vials containing doxycycline hyclate equivalent to 200 mg of doxycycline with 960 mg of ascorbic acid (0049-0980-81).

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com



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