Front

240mm

For the use of Registered Medical Practitioner or Hospital or Laboratory

Metronidazole Injection USP 0.5%w/v

AXAGYL

Composition

Each 100 ml contains:

Metronidazole USP……..……...500mg

Sodium Chloride USP……...0.8%w/v

Water for Injection USP……....q.s

Description

Metronidazole Injection USP contain Metronidazole which is a synthetic antibacterial agent of the nitroimidazole class.

Mechanism of Action

Metronidazole acts by entering in to the cells by passive diffusion and is activated by reductive process. This produces short lived metabolites that damage bacterial DNA and subsequently cause cell death.

Clinical Pharmacology

Metronidazole is a synthetic antibacterial compound. Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of eight hours. The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with fecal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(ß-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m^2.

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess in vitro bactericidal activity against most strains of anaerobic bacteria.

Metronidazole appears in cerebrospinal fluid, saliva and breast milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Plasma concentrations of metronidazole are proportional to the administered dose. An eight-hour intravenous infusion of 100-4,000 mg of metronidazole in normal subjects showed a linear relationship between dose and peak plasma concentration.

In patients treated with intravenous metronidazole, using a dosage regimen of 15 mg/kg loading dose followed six hours later by 7.5 mg/kg every six hours; peak steady-state plasma concentrations of metronidazole averaged 25 mcg/mL with trough (minimum) concentrations averaging 18 mcg/mL.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

In one study newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first three days of life, was inversely related to gestational age. In infants whose gestational ages were between 28 and 40 weeks, the corresponding elimination half-lives ranged from 109 to 22.5 hours.

Microbiology

Metronidazole is active in vitro against most obligate anaerobes, but does not appear to possess any clinically relevant activity against facultative anaerobes or obligate aerobes. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentrations. Metronidazole has been shown to have in vitro and clinical activity against the following organisms:

Anaerobic gram-negative bacilli, including:

Bacteroides species, including the Bacteroides *fragilis* group (B. *fragilis*, B. *distasonis*, B. *ovatus*, B. *thetaiotaomicron*, B. *vulgatus*)

Fusobacterium species

Anaerobic gram-positive bacilli, including:

Clostridium species and susceptible strains of *Eubacterium*

Anaerobic gram-positive cocci, including:

Peptococcus species

Peptostreptococcus species

Susceptibility Tests: Bacteriologic studies should be performed to determine the causative organisms and their susceptibility to metronidazole; however, the rapid, routine susceptibility testing of individual isolates of anaerobic bacteria is not always practical, and therapy may be started while awaiting these results.

Quantitative methods give the most accurate estimates of susceptibility to antibacterial drugs. A standardized agar dilution method and a broth micro dilution method are recommended.

Control strains are recommended for standardized susceptibility testing. Each time the test is performed, one or more of the following strains should be included: *Eubacterium lentum* ATCC 43055, Bacteroides *fragilis* ATCC 25285, and Bacteroides *thetaiotaomicron* ATCC 29741. The mode metronidazole MICs for those three strains are reported to be 0.125, 0.25, and 0.5 mcg/mL, respectively.

A clinical laboratory test is considered under acceptable control if the results of the control strains are within one doubling dilution of the mode MICs reported for metronidazole.

A bacterial isolate may be considered susceptible if the MIC value for metronidazole is not more than 16 mcg/mL. An organism is considered resistant if the MIC is greater than 16 mcg/mL. A report of "resistant" from the laboratory indicates that the infecting organism is not likely to respond to therapy.

Indications

Treatment of Anaerobic Infections

Metronidazole Injection USP is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with Metronidazole therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole.

Metronidazole is effective in Bacteroides fragilis infections resistant to clindamycin, chloramphenicol and penicillin.

Intra-Abdominal Infections, including peritonitis, intra-abdominal abscess and liver abscess, caused by Bacteroides species including the B. *fragilis* group (B. *fragilis*, B. *distasonis*, B. *ovatus*, B. *thetaiotaomicron*, B. *vulgatus*), *Clostridium* species, *Eubacterium* species, *Peptococcus* species and *Peptostreptococcus* species.

Skin and Skin Structure Infections caused by Bacteroides species including the B. *fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species and *Fusobacterium* species.

Gynecologic Infections, including endometritis, endomyometritis, tubo-ovarian abscess and postsurgical vaginal cuff infection, caused by Bacteroides species including the B. *fragilis* group, *Clostridium* species, *Peptostreptococcus* species and *Fusobacterium* species.

Bacterial Septicemia caused by Bacteroides species including the B. *fragilis* group and *Clostridium* species.

Bone and Joint Infections, as adjunctive therapy, caused by Bacteroides species including the B. *fragilis* group.

Central Nervous System (CNS) Infections, including meningitis and brain abscess, caused by Bacteroides species including the B. *fragilis* group.

Lower Respiratory Tract Infections, including pneumonia, empyema and lung abscess, caused by Bacteroides species including the B. *fragilis* group.

Endocarditis caused by Bacteroides species including the B. *fragilis* group.

Prophylaxis

The prophylactic administration of Metronidazole Injection, preoperatively, intraoperatively and postoperatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery, which is classified as contaminated or potentially contaminated.

Prophylactic use of Metronidazole Injection should be discontinued within 12 hours after surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Metronidazole Injection, and other antibacterial drugs, Metronidazole Injection, should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Dosage and Administration

The recommended dosage of Metronidazole Injection USP for the treatment of infections is described below.

Treatment of Anaerobic Infections

The recommended dosage schedule for adults is:

Loading Dose: 15 mg/kg infused over one hour (approximately 1 g for a 70-kg adult).

Maintenance Dose: 7.5 mg/kg infused over one hour every six hours (approximately 500 mg for a 70-kg adult). The first maintenance dose should be instituted six hours following the initiation of the loading dose.A maximum of 4 g should not be exceeded during a 24-hour period.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels and toxicity is recommended.

In patients receiving Metronidazole Injection, in whom gastric secretions are continuously removed by nasogastric aspiration, sufficient metronidazole may be removed in the aspirate to cause a reduction in serum levels.

The dose of Metronidazole Injection should not be specifically reduced in anuric patients since accumulated metabolites may be rapidly removed by dialysis.

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract and endocardium may require longer treatment.

Prophylaxis

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

a.15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery; followed by

b.7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that

- Administration of the initial preoperative dose be completed approximately one hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision.
- Metronidazole Injection, administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Metronidazole Injection should be limited to the day of surgery only, following the above guidelines.

Administration

Metronidazole Injection is to be administered by slow intravenous drip infusion only, either as a continuous or intermittent infusion. Additives should not be

160 mm

Width of Flap=30mm

No. of Flap=8

SIZE: 160 X 240mm

FOR RWANDA

160 mm

Back

240mm

introduced into Metronidazole Injection. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion.
Do not use equipment containing aluminum (e.g., needles, cannulae) that would come in contact with the drug solution.

Contraindications
Metronidazole Injection is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.
Warnings
Central and Peripheral Nervous System Effects:
Convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.
Precautions
General
Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously.
Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering Metronidazole to patients receiving corticosteroids or to patients predisposed to edema.
Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with Metronidazole and requires treatment with a candidacidal agent.
Prescribing Metronidazole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
Laboratory Tests
Metronidazole is a nitroimidazole, and should be used with care in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hemotologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.
Adverse Drug Reactions
The most serious adverse reactions reported in patients treated with metronidazole injection have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity.
The following reactions have also been reported during treatment with Metronidazole Injection, .
Gastrointestinal: Nausea, vomiting, abdominal discomfort, diarrhea and an unpleasant metallic taste.
Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis and stomatitis have occurred; these may be associated with a sudden overgrowth of Candida , which may occur during effective therapy.
Hematopoietic: Reversible neutropenia (leukopenia).
Dermatologic: Erythematous rash and pruritus.
Central Nervous System: Encephalopathy, aseptic meningitis, convulsive seizures, optic neuropathy, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia.
Local Reactions: Thrombophlebitis after intravenous infusion. This reaction can be minimized or avoided by avoiding prolonged use of indwelling intravenous catheters.
Hypersensitivity: Urticaria, erythematous rash, Stevens - Johnson syndrome, flushing, nasal congestion, dryness of the mouth (or vagina or vulva) and fever.
Other: Proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis and fleeting joint pains sometimes resembles “serum sickness.” If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing or headache. A modification of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.
Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for Metronidazole Injection.
“Inform doctors about unexpected reactions after using drugs”

Drug Interactions
Warfarin **and other oral anticoagulants**
Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Metronidazole Injection, USP is prescribed for patients on this type of anticoagulant therapy.
Phenytoin
The simultaneous administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.
Cimetidine
The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

Alcoholic Beverages
Alcoholic beverages should not be consumed during metronidazole therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur.
Disulfiram
disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.
Drug/Laboratory Test Interactions
Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), and lactate dehydrogenase (LDH), triglycerides and hexokinase glucose. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotine adenine dinucleotide (NAD+ºNADH). Interference is due to the similarity in absorbance peaks of NADH (340nm) and metronidazole (322nm) at pH 7.

Pregnancy: Teratogenic Effects
Pregnancy Category B. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. Metronidazole administered intraperitoneally to pregnant mice at approximately the human dose caused fetotoxicity; administered to pregnant mice, no fetotoxicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, these drugs should be used during pregnancy only if clearly needed.
Lactation
Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in breast milk in concentrations similar to those found in plasma.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Overdosage
Use of dosages of intravenous metronidazole higher than those recommended has been reported. These include the use of 27 mg/kg three times a day for 20 days, and the use of 75 mg/kg as a single loading dose followed by 7.5 mg/kg maintenance doses. No adverse reactions were reported in either of the two cases.
Treatment: There is no specific antidote for overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

Storage
Store below 30°C. Protect from light. Do not refrigerate or freeze.

Presentation: 1 x 100ml LDPE bottle packed in unit carton, along with pack insert.

Manufactured In India by:
Axa Parenterals Ltd.
Plot No. 936, 937 & 939, Vill. Kishanpur, Jamalpur,
Roorkee-247667, Distt. Haridwar (Uttarakhand)

Width of Flap=30mm
No. of Flap=8
SIZE: 160 X 240mm
FOR RWANDA

Product Name	Country	Revision No.	Date	Size (mm)
AXAGYL 100 ML	RWANDA	00	23.10.19	160 X 240

App. by	INT MARKETING	DRA	Production	QC	QA