INDICATIONS AND USAGE

Treatment of Anaerobic infections

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

ABAGYL I.V 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 ABAGYL I.V 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 ABAGYL I.V should be discontinued within 12 hours after surgery. If there are signs of infection, specimen for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see Dosage and Administration).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ABAGYL I.V. and other antibacterial drugs, ABAGYL I.V 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.

CONTRAINDICATIONS

ABAGYL I.V. is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

WARNINGS

Convulsive seizures 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

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 ABAGYL I.V. to patients receiving corticosteroids or to patients predisposed to edema.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with ABAGYL I.V. and requires treatment with an appropriate agent.

Prescribing ABAGYL I.V 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.

DRUG INTERACTIONS

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 ABAGYL I.V. is prescribed for patients on this type of anticoagulant therapy.

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.

ABAGYL I.V

(Metronidazole)

For intravenous infusion

Rx only

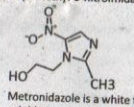
apdl

COMPOSITION

Each 100ml contains:
Metronidazole B.P. ..... 0.5 g
Water for injections B.P ..... q.s

DESCRIPTION

Metronidazole Injection,, B.P is a synthetic antimicrobial agent for intravenous (I.V.) administration. Metronidazole, a nitroimidazole, is 2-(2-Methyl-5-nitroimidazol-1-yl)ethanol. Its empirical formula is $C_6H_9N_3O_3$ and its chemical structure is:



Metronidazole is a white to pale yellow, odorless crystalline powder with a molecular weight of 171.2. It darkens on exposure to light, and is slightly soluble in water and alcohol.

CLINICAL PHARMACOLOGY

Metronidazole in ABAGYL I.V has similar disposition as oral 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

DOSAGE AND ADMINISTRATION

In elderly patients the pharmacokinetics of metronidazole may be altered and therefore monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

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.

Parenteral therapy may be changed to oral metronidazole when conditions warrant, based upon the severity of the disease and the response of the patient to ABAGYL I.V. treatment. The usual adult oral dosage is 7.5 mg/kg every six hours.

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 ABAGYL I.V. 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 ABAGYL I.V. should not be specifically reduced in anuric patients since accumulated metabolites maybe 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 commended dosage schedule for adults is:

I. 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery, followed by;
II. 7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) 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, and (2) ABAGYL I.V. be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of ABAGYL I.V. should be limited to the day of surgery only, following the above guidelines.

Caution

ABAGYL I.V. is to be administered by slow intravenous drip infusion only, either as a continuous or intermittent infusion. Additives should not be introduced into ABAGYL I.V. 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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Presentation

Clear, almost colorless to pale yellow solution in sterile plastic bottle of 100ml

Shelf life

The manufacturing and expiry dates are indicated on the packaging.

Storage

Store below 30º C but do not freeze, protect from light.

Registration Number(s)	:	7544/06/11
Date of first Authorization	:	05th January 2012
Date of Revision	:	04th January 2017
Next Date of Revision	:	04th January 2020

Manufactured by:

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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 should not be consumed during metronidazole therapy because abdominal cramps, nausea, vomiting, headaches and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and 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), 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+ ⊠ NADH). Interference is due to the similarity in absorbance peaks of NADH (340nm) and metronidazole (322nm) at pH 7.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Tumorigenicity in Rodents - Metronidazole has shown evidence of carcinogenic activity in studies involving chronic, oral administration in mice and rats, but similar studies in the hamster gave negative results. Also, metronidazole has shown mutagenic activity in a number of invitro assay systems, but studies in mammals (in vivo) failed to demonstrate a potential for genetic damage.

PREGNANCY AND BREAST FEEDING

Teratogenic effect

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 intra-peritoneally to pregnant mice at approximately the human dose caused fetotoxicity while that administered orally 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.

Nursing Mothers

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.

INFORMATION FOR PATIENTS

Patients should be counseled that antibacterial drugs including ABAGYL I.V. should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ABAGYL I.V. is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may:

1. Decrease the effectiveness of the immediate treatment.
2. Increase the likelihood that bacteria will develop resistance and will not be treatable by ABAGYL I.V. or other antibacterial drugs in the future.

ADVERSE REACTIONS

Two serious adverse reactions reported in patients treated with intravenous metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged oral administration of metronidazole, patients should be observed carefully if neurologic symptoms occur and a prompt evaluation made of the benefit/risk ratio of the continuation of therapy.

The following reactions have also been reported during treatment with Metronidazole:

Gastrointestinal: Nausea, vomiting, abdominal discomfort, diarrhea and an unpleasant metallic taste.

Hematopoietic: Reversible neutropenia (leukopenia).

Dermatologic: Erythematous rash and pruritus.

Central Nervous System: Headache, dizziness, syncope, ataxia and confusion.

Local Reactions: Thrombophlebitis after intravenous infusion. This reaction can be minimized or avoided by avoiding prolonged use of in-dwelling intravenous catheters.

Other: Fever. Instances of a darkened urine have also been reported, and this manifestation has been the subject of a special investigation.

Treatment of over dosage: There is no specific antidote for overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.