For the use of a Registered Medical Practitioner only

Unique's metrogyl® Injection (5mg/ml) Isotonic

Rx Metronidazole Injection IP

(For Intravenous administration)

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided.

COMPOSITION

Each 100 ml contains:

Metronidazole IP.....500 mg

Water for Injection IP……..q.s.

DOSAGE FORM

Solution for injection

THERAPEUTIC INDICATIONS

Metrogyl* Injection 5mg/ml is indicated in adults and children when oral medication is not possible for the following indications:

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

Metrogyl injection 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, Peptococcus 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 Metrogyl injection preoperatively, intra-operatively, and postoperatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Metrogyl injection and other antibacterial drugs, Metrogyl injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

PSOLOGY AND METHOD OF ADMINISTRATION

Method of Administration

Metronidazole 5mg/ml Intravenous Infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bottle infused over 20 to 60 minutes). Oral medication should be substituted as soon as feasible.

The solution is to be inspected visually for particulate matter and discolouration prior to administration and should only be used if it is clear and free from particles.

Anaerobic infections:

Intravenous route is to be used initially if patient symptoms preclude oral therapy. Various schedules are possible.

Adults: 1000mg-1500mg daily as a single dose or alternatively 500mg every 8 hours.

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg. Depending on the severity of the infection. Duration of treatment is usually 7 days.

Children < 8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5 mg/kg every 12 hours.

In newborns with a gestation age < 40 weeks, accumulation of metronidazole can occur during the first week of life; therefore the concentrations of metronidazole in serum should preferably be monitored after a few days of therapy.

Oral medication could be given, at the same dose regimen. Oral medication should be substituted as soon as feasible.

Duration of Treatment

Treatment for seven to ten days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician might decide to prolong treatment e.g.; for the eradication of infection from sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or genital tract.

Bacterial vaginosis:

Adolescents: 400 mg twice daily for 5-7 days or 2000 mg as a single dose.

Urogenital trichomoniasis:

Adults and adolescents: 2000 mg as a single dose or 200 mg 3 times daily for 7 days or 400 mg twice daily for 5-7 days.

Children < 10 years: 40 mg/kg orally as a single dose or 15 – 30 mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000 mg/dose.

Giardiasis:

> 10 years: 2000 mg once daily for 3 days, or 400 mg three times daily for 5 days, or 500 mg twice daily for 7 to 10days

Children 7 to 10 years: 1000 mg once daily for 3 days
Children 3 to 7 years: 600 to 800 mg once daily for 3 days
Children 1 to 3 years: 500 mg once daily for 3 days

Alternatively, as expressed in mg per kg of body weight: 15-40 mg/kg/day divided in 2-3 doses.

Amoebiasis:

> 10 years: 400 to 800 mg 3 times daily for 5-10 days

Children 7 to 10 years: 200 to 400 mg 3 times daily for 5-10 days
Children 3 to 7 years: 100 to 200 mg 4 times daily for 5-10 days
Children 1 to 3 years: 100 to 200 mg 3 times daily for 5-10 days

Alternatively, doses may be expressed by body weight 35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day.

Prophylaxis against postoperative infections caused by anaerobic bacteria:

Primarily in the context of abdominal, (especially colorectal) and gynaecological surgery

Antibiotic prophylaxis duration should be short, mostly limited to the post-operative period (24 hours but never more than 48 hours). Various schedules are possible.

Adults: Intra-venous injection of single dose of 1000mg-1500mg, 30-60 minutes preoperatively or alternatively 500mg immediately before, during or after operation, then 500mg 8 hourly.

Children < 12 years: 20-30 mg/kg as a single dose given 1-2 hours before surgery

Newborns with a Gestation age <40 weeks: 10 mg/kg body weight as a single dose before operation

Elderly Population

Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Patients with renal failure

Routine adjustments of the dosage of Metronidazole are not considered necessary in the presence of renal failure.

No routine adjustment in the dosage of Metronidazole needs to be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD). However, dosage reduction may be necessary when excessive concentrations of metabolites are found.

In patients undergoing haemodialysis, Metronidazole should be re-administered immediately after haemodialysis.

Patients with advanced hepatic insufficiency

In patients with advanced hepatic insufficiency a dosage reduction with serum level monitoring is necessary.

CONTRAINDICATIONS

Known hypersensitivity to Metronidazole or other imidazole derivatives or any of the excipients.

Metronidazole is contraindicated in the first trimester of pregnancy.

Use of Metronidazole is contraindicated in patients with end stage liver damage, haematopoietic disorders and uncontrolled diseases of the central or peripheral nervous system.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Liver disease:

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit ratio of using Metronidazole to treat trichomoniasis in such patients should be carefully considered. Plasma levels of Metronidazole should be closely monitored.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

Active Central Nervous System disease:

Metronidazole should be used with caution in patients with active disease of the Central Nervous System. The treatment should be withdrawn in case of ataxia, dizziness, or confusion. The risk of aggravation of the neurological state should be considered in patients suffering from severe central and peripheral neurological diseases, fixed or progressive paraesthesia and epilepsy. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Alcohol:

Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like effect (flushing, vomiting, tachycardia).

Intensive or prolonged Metronidazole therapy:

As a rule, the usual duration of therapy with i.v Metronidazole or other imidazole derivatives is usually less than 10 days. This period may only be exceeded in individual cases after a very strict benefit-risk assessment. Only in the rarest possible case should the treatment be repeated.

Limiting the duration of treatment is necessary because damage to human germ cells cannot be excluded.

Intensive or prolonged Metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible.

In case of prolonged treatment, occurrence of undesirable effects such as paraesthesia, ataxia, dizziness and convulsive crises should be checked. High dose regimes have been associated with transient epileptiform seizures.

Fungal Superinfections:

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Renal Impairment:

Patients with end-stage renal disease may excrete metronidazole and metabolites slowly in the urine, resulting in significant accumulation of metronidazole metabolites. Monitoring for metronidazole associated adverse events is recommended.

Drug-Resistant Bacteria and Parasites:

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Monitoring:

Regular clinical and laboratory monitoring (including leukocyte formula) are advised in cases of high-dose or prolonged treatment, in case of antecedents of blood dyscrasia, in case of severe infection and in severe hepatic insufficiency.

General:

Patients should be warned that Metronidazole may darken urine (due to Metronidazole metabolite).

DRUG INTERACTIONS

Not recommended concomitant therapy:

Alcohol: Disulfram-like effect (warmth, redness, vomiting, tachycardia). Alcohol beverage and drugs containing alcohol should be avoided. Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).

Concomitant therapy requiring special precautions:

Oral anticoagulants (warfarin): increase of the effects of oral anticoagulants and the risk of haemorrhage (decrease in its liver catabolism). Prothrombin time should be monitored more frequently. The dose of oral anticoagulants should be adjusted during the treatment with Metronidazole and 8 days after withdrawal.

A large number of patients have been reported showing an increase in oral anticoagulant activity whilst receiving concomitant antibiotic therapy. The infectious and inflammatory status of the patient, together with their age and general well-being are all risk factors in this context. However, in these circumstances it is not clear as to the part played by the disease itself or its treatment in the occurrence of prothrombin time disorders. Some classes of antibiotics are more likely to result in this interaction, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins.

Vecuronium (non depolarising curaremimetic): Metronidazole can potentialise the effects of vecuronium.

Combinations to be considered:

5 Fluoro-uracile: increase in the toxicity of 5 fluoro-uracile due to a decrease of its clearance.

Lithium: lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and Metronidazole. Lithium treatment should be tapered or withdrawn before administering Metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive Metronidazole.

Barbiturates: Phenobarbital might induce the metabolism of Metronidazole, which could lead to decreased efficacy of Metronidazole.

Cholestyramine may delay or reduce the absorption of Metronidazole.

Concomitant administration of phenytoin and Metronidazole may affect the metabolism of Metronidazole.

Cimetidine inhibits the metabolism of Metronidazole.

Cyclosporine: Case reports indicate that concomitant treatment with Metronidazole and Cyclosporine might lead to increased serum levels of cyclosporine. Cyclosporine concentrations and creatinine levels should be monitored.

Busulfan: Plasma concentrations of busulfan may increase during concomitant treatment with metronidazole, which can result in serious busulfan toxicity.

Laboratory tests:

Metronidazole may immobilise Treponema and thus may lead to falsely positive Nelson's test.

USE IN SPECIFIC POPULATIONS

Pregnancy

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 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, this drug should be used during pregnancy only if clearly needed. Metronidazole is contraindicated in the first trimester of pregnancy.

Lactation

Metronidazole is secreted in human milk in concentrations similar to those found in plasma. 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.

UNDESIRABLE EFFECTS

Common undesirable effects (>1/100 <1/10): gastrointestinal tract: diffuse symptoms of intolerance (like nausea, vomiting), metallic taste, stomatitis and glossitis and dry mouth; myalgia.

Uncommon undesirable effects (>1/1000, <1/100): leucopenia, headaches and weakness.

Rare undesirable effects (>1/10,000, <1/1000):

General: fever, skin rashes, urticaria, erythema multiforme anaphylactic shock, Quincke oedema, pustolosis, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

Neurology: drowsiness, dizziness, ataxia, peripheral neuropathy or transient epileptiform seizures, hallucinations, Encephalopathy, optic neuropathy and aseptic meningitis.

Blood: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia. Blood dyscrasia is generally reversible but fatal cases have been reported.

Liver: Abnormal function tests, cholestatic hepatitis jaundice, pancreatitis; rare and reversible cases of pancreatitis are reported.

Gastrointestinal: Mucositis, epigastralgia, nausea, vomiting, diarrhoea, anorexia.

Urine: darkening of urine.

Eyes: diplopia, myopia.

Herxheimer reaction:

Changes in the blood picture as well as peripheral neuropathy observed after prolonged treatment or high dosages generally abate after treatment withdrawal.

Frequency, type and severity of adverse reactions in children are the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbcpl.com

OVERDOSE

Symptoms

In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting, ataxia and slight disorientation. In a preterm newborn, no clinical or biological sign of toxicity developed.

Treatment

There is no specific treatment for Metronidazole overdose, Metronidazole infusion should be discontinued. Patients should be treated symptomatically.

CLINICAL PHARMACOLOGY

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use: imidazole derivatives

And

Pharmacotherapeutic group: Antiprotozoals: nitroimidazole derivatives

Mechanism of action

Metronidazole is an anti-infectious drug belonging to the pharmacotherapeutic group of nitroimidazole derivatives, which have effect mainly on strict anaerobes. This effect is probably caused by interaction with DNS and different metabolites.

Pharmacodynamic properties

Metronidazole is an anti-infectious drug belonging to the pharmacotherapeutic group of nitroimidazole derivatives, which have effect mainly on strict anaerobes. This effect is probably caused by interaction with DNS and different metabolites.

Metronidazole has antibacterial and antiprotozoal actions and is effective against anaerobic bacteria and against Trichomonas vaginalis and other protozoa including Entamoeba histolytica and Giardia lamblia.

Anti-Microbial Spectrum:

The MIC breakpoints separating susceptible from intermediately susceptible and intermediately susceptible from resistant organisms are as following:

S $\leq$ 4 mg/l and R > 4 mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to Metronidazole or not.

Categories
SUSCEPTIBLE
Gram negative aerobes
Helicobacter pylori
Anaerobes
Bacteroides fragilis
Bifidobacterium>>resistant (70%)
Bilophila
Clostridium
Clostridium difficile
Clostridium perfringens
Eubacterium
Fusobacterium
Peptostreptococcus
Prevotella
Porphyromonas
Veillonella
RESISTANT
Gram positive aerobes
Actinomyces
Anaerobes
Mobiluncus
Propionibacterium acnes
ANTIPARASITIC ACTIVITY
Entamoeba histolytica
Giardia intestinalis
Trichomonas vaginalis

Cross–resistance with tindazol occurs.

Pharmacokinetic properties

Distribution: After administration of a single 500 mg dose, mean metronidazole peak plasma concentrations of ca. 14 –18 µg/ml are reached at the end of a 20 minute infusion. 2-hydroxy-metabolite peak plasma concentrations of ca. 3 µg/ml are obtained after a 1 g single i.v. dose. Steady state Metronidazole plasma concentrations of about 17 and 13 µg/ml are reached after administration of Metronidazole every 8 or 12 hours, respectively.

Plasma protein binding is less than 10%, and the volume of distribution 1.1 ± 0.4 l/kg.

Metabolism: Metronidazole is metabolised in the liver by hydroxylation, oxidation and glucuronidation. The major metabolites are a 2-hydroxyand an acetic acid metabolite.

Elimination: More than 50% of the administered dose is excreted in the urine, as unchanged Metronidazole (ca. 20% of the dose) and its metabolites. About 20% of the dose is excreted with faeces. Clearance is 1.3 ± 0.3 ml/min/kg, while renal clearance is about 0.15 ml/min/kg. The plasma elimination half-life of Metronidazole is ca. 8 hours, and of the 2-hydroxy-metabolite ca. 10 hours.

Special patient groups: The plasma elimination half-life of Metronidazole is not influenced by renal impairment, however this may be increased for 2-hydroxy- and an acetic acid metabolite. In the case of haemodialysis, Metronidazole is rapidly excreted and the plasma elimination half-life is decreased to ca. 2.5 h. Peritoneal dialysis does not appear to affect the elimination of Metronidazole or its metabolites. In patients with impaired liver function, the metabolism of Metronidazole is expected to decrease, leading to an increase in the plasma elimination half-life. In patients with severe liver impairment, clearance may be decreased up to ca. 65%, resulting in an accumulation of Metronidazole in the body.

NONCLINICAL TOXICOLOGY

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 in vitro assay systems, but studies in mammals (in vivo) failed to demonstrate a potential for genetic damage.

DESCRIPTION

Metronidazole is an anti-infectious drug belonging to the pharmacotherapeutic group of nitroimidazole derivatives, which have effect mainly on strict anaerobes. Chemical name is 2-Methyl-5-nitroimidazole-1-ethanol.

INCOMPATABILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal product except for those mentioned below.

In patients maintained on intravenous fluids, Metronidazole 5mg/ml Intravenous Infusion may be diluted with appropriate volumes of 0.9% sodium chloride solution, dextrose 5% - 0.9% sodium chloride solution, dextrose 5% w/v or potassium chloride infusions (20 and 40 mmol/litre).

STORAGE AND HANDLING INSTRUCTIONS:

Store in a dark place until ready for use.

PACKAGING INFORMATION:

Metrogyl Injection Isotonic (for intravenous injection) is available in bottle of 100ml.

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road,
Worli, Mumbai - 400 030. India.

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Note: This prescribing information is applicable for India Market only.