

Data Sheet

METRONIDAZOLE

Metronidazole Intravenous Infusion 500mg/100mL (Viaflex®Minibag)

Description

Metronidazole is 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole B.P. It appears as a white to brownish cream crystalline substance with melting point 159-162C. Solubility in water at 20C is 1 g/100mL; in ethyl alcohol, 0.5g/100mL; in chloroform, 0.4g/100mL; slightly soluble in ether and soluble in dilute acids. When reconstituted as Metronidazole IV for Infusion, it has a pH of between 4.8 and 5.2.

Composition

Metronidazole 500mg/100mL Infusion (Viaflex® Minibag): Each mL contains: metronidazole B.P. 5mg, anhydrous citric acid B.P. 0.4mg (equivalent to citric acid monohydrate 0.44mg/mL), sodium phosphate B.P. 1.5mg and sodium chloride B.P. 7.4mg. Each mL contains 0.135mmol of sodium.

Classification and Activity

Metronidazole is a nitroimidazole antiinfective agent which has specific activity against a number of obligate anaerobic organisms and protozoa.

Pharmacology

Mode of Action

Metronidazole is bactericidal, amoebicidal and trichomonocidal. The exact mode of action has not been fully elucidated. Metronidazole is reduced by low-redox-potential electron transfer proteins (eg. nitroreductases such as ferredoxin) to unidentified polar product(s) which lack the nitro group. The reduction product(s) appears to be responsible for the cytotoxic and antimicrobial effects of the drug which include disruption of DNA and inhibition of nucleic acid synthesis.

Microbiology

Metronidazole is bactericidal in vitro against many anaerobic gram-negative bacilli including Bacteroides fragilis and other Bacteroides species; also other species including Fusobacterium. The drug is effective against many anaerobic gram-positive cocci including Clostridium species, Eubacterium, and anaerobic Streptococcus. The MIC for susceptible anaerobes is <6.2 micrograms/mL. Serum levels higher than this are achieved at the recommended doses.

Metronidazole is also active against a wide range of pathogenic protozoa including Trichomonas vaginalis and other trichomonads, Entamoeba histolytica, Giardia lamblia, Balantidium coli and the causative organisms of acute ulcerative gingivitis.

Metronidazole is ineffective against both aerobic and facultative anaerobic bacteria.

Pharmacokinetics

Bioavailability

For both oral and intravenous administration, the area under the plasma clearance curve is equivalent.

Absorption

Maximum plasma concentrations occur at the conclusion of the infusion after intravenous administration. Traces are detected after 24 hours. The biological half-life of a single intravenously administered dose of metronidazole has been determined as 7.3 hours 1.0 hours.

Distribution

Metronidazole is widely distributed in body tissues and fluids. It diffuses across the blood-brain barrier, crosses the placenta and appears in the saliva and breast milk of nursing mothers in concentrations equivalent to those found in the plasma. It attains therapeutic concentrations in the bile and the CSF.

Plasma Protein Binding

Metronidazole is not significantly bound to plasma protein.

Metabolism

An oral or intravenous dose of metronidazole is partially metabolised in the liver by hydroxylation, acid side-chain oxidation and glucuronide conjugation. The major metabolite, 2-hydroxymethyl metronidazole, has some antiprotozoal activity in vitro.

Excretion

Approximately three-fourths of a single 750mg oral dose is excreted as nitro-containing compounds (unchanged drug and its metabolites) in the urine within 5 days. Most of the remainder is excreted in the faeces. Urine may be dark or reddish brown in colour following oral and IV administration of the drug due to the presence of water-soluble pigments, which result from its metabolism.

Indications

Metronidazole intravenous infusion is indicated:

- 1. For treatment of anaerobic infections in patients for whom oral administration is not possible.*
- 2. When immediate anti-anaerobic therapy is required.*
- 3. Where prophylactic cover is required at lower abdominal surgical sites presumed contaminated or potentially contaminated by anaerobic micro-organisms. Procedures of this type include appendicectomy, colonic surgery, vaginal hysterectomy, abdominal surgery in the presence of anaerobes in the peritoneal cavity and surgery performed in the presence of anaerobic septicaemia.*

Note: Metronidazole is inactive against aerobic or facultative anaerobic bacteria.

Contraindications

Metronidazole is contraindicated:

- 1. in patients with evidence of or a history of blood dyscrasias. (Occasionally a mild leukopenia has been observed during administration; however no persistent haematological abnormalities have been observed in animals or clinical studies.)*
 - 2. in the presence of active organic disease of the central nervous system.*
 - 3. in patients who are hypersensitive to metronidazole or other nitroimidazoles.*
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Warnings and Precautions

Warning

Metronidazole has been shown to be carcinogenic in mice and rats. Its use, therefore, should be reserved for the conditions described in the Indications section.

Central and Peripheral Nervous System Effects

Encephalopathy and peripheral neuropathy: Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.

Encephalopathy has been reported in association with cerebellar toxicity characterised by ataxia, dizziness and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS systems are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.

Peripheral neuropathy, mainly of sensory type has been reported and is characterised by numbness or parenthesis of the extremities.

Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis: Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

The appearance of abnormal neurological signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

Candidiasis

Fungal overgrowth of the gastrointestinal or genital tract may occur during the metronidazole therapy and require treatment with an antifungal drug effective against candida.

Long Term Therapy

If metronidazole is administered for more than ten days, it is recommended that haematological tests, especially total and differential leucocyte counts, be carried out regularly and that patients be monitored for adverse reactions such as peripheral neuropathy. If leukopenia or abnormal neurological signs occur, the drug should be discontinued immediately.

Surgical Drainage

Use of metronidazole does not obviate the need for drainage of pus whenever indicated such as in amoebic liver abscess or abscess in other accessible positions.

Sodium Retention

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering Metronidazole IV to patients receiving corticosteroids or patients predisposed to oedema. Refer to Interaction with other Drugs.

Impaired Renal Function

In patients being haemodialysed twice weekly, metronidazole and its major metabolite are rapidly removed during an eight hour period of dialysis, so that the plasma concentration quickly falls below the therapeutic range. Hence a further dose of metronidazole would be needed after dialysis to restore an adequate plasma concentration. In patients with renal failure, the half-life of metronidazole is unchanged, but those of its major metabolites are prolonged 4-fold or greater. The accumulation of the 2-hydroxymethyl metabolite could be associated with side effects and measurement of its plasma concentration by high pressure liquid chromatography (HPLC) has been recommended.

In the absence of haemodialysis, the plasma clearance and elimination half-life of metronidazole are equivalent to those in patients with normal renal clearance so dosage adjustment is not necessary.

While the pharmacokinetics of metronidazole is little changed in the anuric patient, the metabolites are retained; the clinical significance of this is unknown.

Impaired Hepatic Function

information is available. Since metronidazole is partly metabolised in the liver, caution should be exercised in patients whose liver function is impaired. Close monitoring of plasma metronidazole levels and toxicity is recommended.

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 haematological abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.

Use in Pregnancy (Category B2)

Metronidazole should not be given in the first trimester of pregnancy since it crosses the placenta and rapidly enters the foetal circulation. Although it has not been shown to be teratogenic in either human or animal studies, such a possibility cannot be excluded.

Use of metronidazole for trichomoniasis in the second and third trimesters should be restricted to those in whom local palliative treatment has been inadequate to control symptoms.

Mutagenicity, tumorigenicity

In studies on the mutagenic potential of metronidazole, the Ames mutagenicity test was positive, while several nonbacterial tests in animals were negative. In patients suffering from Crohn's Disease, metronidazole increased chromosome abnormalities. In addition, the drug has been shown to be tumorigenic in rodents. The benefit/risks should, therefore, be carefully assessed in each case particularly in relation to the severity of the disease and the age of the patient.

Carcinogenicity

Metronidazole has shown evidence of tumorigenic activity in a number of studies involving chronic oral administration in mice and rats. Most prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in multiple studies, including one in which the animals were dosed on an intermittent schedule (every fourth week only). The results of one of the mouse studies indicates a statistically significant increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding.

In the rat, there was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumours, among females fed metronidazole on a lifetime basis, over that observed in concurrent female control groups.

Two lifetime tumorigenicity studies have been performed in hamsters; in both cases the results were negative.

*A retrospective study of 771 women treated with metronidazole for *Trichomonas vaginalis* has revealed no statistically significant increase in cancer incidence over that expected in the normal population. An apparent increase in the incidence of cervical carcinoma observed in the metronidazole-treated group was no different from the incidence observed in women documented to have had trichomoniasis not treated by metronidazole.*

Use in Lactation

Metronidazole is secreted in breast milk. In view of the drug's tumorigenic and mutagenic potential, breastfeeding is not recommended.

Lithium

Lithium toxicity may occur in patients who are being treated with high doses of lithium. Refer to Interaction with other Drugs section.

Interactions With Other Drugs

Coumarin Anticoagulants: Oral or IV metronidazole potentiates the effects of oral anticoagulants resulting in prolongation of prothrombin time; concurrent administration should be avoided if possible. If metronidazole is used in patients receiving an oral anticoagulant, prothrombin times should be monitored and the dosage of the anticoagulant adjusted accordingly.

Alcohol: Metronidazole appears to inhibit alcohol dehydrogenase and other alcohol oxidising enzymes. Mild disulfiram-like reactions including flushing, headache, nausea, vomiting, abdominal cramps and sweating have occurred in patients ingesting alcohol while being treated with metronidazole.

Patients should be advised not to take alcohol during therapy or for at least one day afterwards because of the possibility of a disulfiram-like reaction.

Disulfiram: Administration of disulfiram with metronidazole has been associated with acute psychoses and confusion in some patients; therefore the two drugs should not be administered. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Cyclosporin: There is a risk of cyclosporin serum levels increasing when it is used in combination with metronidazole. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

5-flourouracil: Metronidazole used in combination with 5-flourouracil may lead to reduced clearance of 5-flourouracil, resulting in increased toxicity.

Phenobarbital and Phenytoin: The simultaneous administration of drugs which induce microsomal liver enzyme activity, such as phenobarbital, pentobarbital and phenytoin may accelerate the elimination of metronidazole, resulting in reduced plasma concentrations and increased concentrations of its 2-hydroxymethyl metabolite; impaired clearance of phenytoin has also been reported.

Lithium: Initiation of short-term metronidazole therapy in patients stabilised on relatively high dosage of lithium has been reported to increase serum lithium concentrations, resulting in signs of lithium toxicity in several patients. Serum lithium and serum creatinine levels should be obtained several days after commencing metronidazole therapy to detect any increase that may precede clinical symptoms of lithium intoxication.

Cimetidine: Simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease the plasma clearance of metronidazole. It is not clear if ranitidine exerts a similar effect.

Corticosteroids: Care should be taken when administering metronidazole infusion to patients receiving corticosteroid therapy or to patients predisposed to oedema since administration of solutions containing sodium ions may result in sodium retention.

Cyclophosphamide and Carmustine (BCNU): Metronidazole should be used with caution in patients who are receiving cyclophosphamide or carmustine as a drug interaction demonstrated in mice leads to increased toxicity.

Fluorouracil and Azathioprine: Transient neutropenia has been reported in 12 patients who received oral and IV metronidazole in conjunction with IV fluorouracil and in at least 1 patient who received oral metronidazole in conjunction with azathioprine.

Compatibility with Intravenous Infusions and Other Drugs

Metronidazole infusion may be diluted to 1 in 5 or greater with appropriate volumes of Sodium Chloride 0.9%, Glucose-Saline combinations, Glucose 5% or potassium chloride injections 20mmol/L and 40mmol/L. While physically compatible with Compound Sodium Lactate Infusion (Hartmann's Solution) and Compound Sodium Chloride Infusion (Ringer's Solution), metronidazole is not chemically compatible with them over extended periods of time. Therefore addition of metronidazole infusion to these solutions is not recommended. However, it may be delivered through the administration set Y-site of fast-running infusions of Hartmann's or Ringer's Solutions. While Glucose 10% is compatible with metronidazole infusion, its use as a diluent and vehicle is not recommended because of the high osmolarity of the resulting solution.

Metronidazole infusion is incompatible with aluminium; do not use equipment containing aluminium components (eg., needle or cannula hubs). Other drugs should not be added directly to metronidazole infusion.

Interference with Laboratory Tests

Metronidazole may interfere with AST (SGOT), ALT (SGPT), LDH, triglycerides, or glucose determinations when these are based on the decrease in ultraviolet absorbance which occurs when NADH is oxidised to NAD. Metronidazole interferes with these assays because the drug has an absorbance peak of 322nm at pH 7 which is close to the 340nm absorbance peak of NADH; this causes an increase in absorbance at 340 nm resulting in falsely decreased values.

Adverse Reactions

Gastrointestinal

When administered orally or intravenously, metronidazole is well tolerated. The most common adverse reactions have involved the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia and occasionally vomiting, diarrhoea,

epigastric distress and abdominal cramping; constipation and oral mucositis have also been reported. A metallic, sharp unpleasant taste is not unusual. Furry tongue, glossitis and stomatitis have occurred; these may be associated with Candida overgrowth. Proliferation of Candida may also occur in the vagina. Refer to warnings and precautions section.

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.

Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. Rare cases of pancreatitis, abating on withdrawal of the drug, have been reported.

There have been a number of reports both in Australia and in overseas literature of cases of pseudomembranous colitis whilst on metronidazole therapy.

Haematological

A moderate and transient leukopenia may occasionally be observed. If this occurs, the total leukocyte count may be expected to return to normal after the course of medication is completed. One case of bone marrow aplasia has been reported. If profound bone marrow suppression occurs, use of metronidazole should be ceased and appropriate supportive therapy instituted. Very rare cases of agranulocytosis and neutropenia have been reported. Rarely, reversible thrombocytopenia occurs.

Thrombophlebitis has been reported after intravenous infusion. This reaction can be minimised or avoided by limiting the duration of infusion and frequent resiting of the indwelling IV cannula.

Neurological

The most serious adverse reactions in patients treated with metronidazole injection have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy.

Lack of coordination and ataxia have been reported. Confusion, irritability, depression, weakness, and insomnia have been experienced as has peripheral neuropathy, characterised mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged metronidazole therapy, such subjects should be specifically warned about these reports and told to stop the drug and report immediately if any neurological symptoms occur.

Headache, dizziness, syncope and dysarthria have also been reported. Transient vision disorders such as diplopia and myopia have been reported.

Psychotic reactions have been reported in alcoholic patients receiving metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram in the previous two weeks.

Liver

Very rare cases of reversible abnormal liver function tests and cholestatic hepatitis have been reported.

Auditory and vestibular

Dizziness, vertigo, and tinnitus have been reported.

Dermatological

Erythematous rash and pruritus.

Hypersensitivity

Urticaria, erythematous rash, Stevens-Johnson Syndrome, flushing, nasal congestion, dryness of mouth (or vagina or vulva), fever, angioedema and rare anaphylactic shock have been reported.

Musculo-skeletal

Fleeting joint pains sometimes resembling "serum sickness" have been reported.

Urogenital

Dysuria, cystitis and a sense of pelvic pressure have been reported. Very rarely, dyspareunia, fever, polyuria, incontinence, decrease in libido, proctitis and pyuria have occurred in patients receiving the drug. Instances of darkened urine have been reported and this manifestation has been the subject of investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it almost certainly is a metabolite of metronidazole. It seems certain that it is of no clinical significance and may be encountered only when metronidazole is administered in higher than recommended doses.

Cardiac

Flattening of the T-wave and prolongation of the QT interval may be seen in ECG tracings.

Other

Instances of a darkened urine have also been reported, and this manifestation has been the subject of a special investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Dosage and Administration

A maximum of 4g should not be exceeded in a 24 hour period. For prophylactic use, the appropriate dose should be infused shortly before surgery and repeated every eight hours for the next 24 hours. Dosages should be decreased in patients with severe hepatic disease; plasma metronidazole levels should be monitored. In elderly patients, the pharmacokinetics of metronidazole may be altered; therefore monitoring of serum levels may be necessary to adjust metronidazole dosage accordingly.

Metronidazole should be infused intravenously at a rate of 5mL (25mg) per minute. Metronidazole infusion may be administered alone or concurrently (but separately) with other bacteriologically appropriate parenteral antibacterial agents. Other IV drugs or infusions should, if possible, be discontinued during its administration. While the solution should be protected from direct sunlight during administration, exposure to fluorescent light for short periods will not result in its degradation.

Do not use plastic infusion bags in series connections. This practice could result in air embolism due to air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Adults and children over 12 years

100mL containing 500mg Metronidazole B.P. by intravenous infusion every eight hours.

Children under 12 years

As for adults, but a single intravenous dose is based on 1.5mL (7.5mg metronidazole)/kg body weight.

The Elderly

Use the adult dose with care. As some degree of hepatic or renal impairment may be present, see the appropriate sections above.

Duration of therapy

Treatment for seven days should be satisfactory for most patients but, depending upon clinical and bacteriological assessment, the clinician may decide to prolong treatment, e.g. for the eradication of infection from sites which cannot be drained or are prone to

endogenous recontamination by anaerobic pathogens from the gut, nasopharynx or the female genital tract. Oral metronidazole should be substituted as soon as possible.

Instructions to be given to the Patient

1. Patients, especially pregnant women, should be warned to refrain from alcohol whilst taking metronidazole.
2. Patients should be advised to report any signs of toxicity, especially neurological disturbances, to their doctor.
3. Patients should be warned about the possibility of their urine darkening in colour.

NOTES:

Prevention of infection at the surgical site requires adequate tissue concentration of the drug being attained at the time of surgery. The dose and route of administration should be selected in each case to achieve this objective.

Although metronidazole has been used in children for some years, recent evidence concerning mutagenicity and tumorigenicity suggests caution be exercised when using the metronidazole in this age group.

In infants and other patients maintained on intravenous infusions, metronidazole may be diluted 1 in 5 or greater with isotonic intravenous infusions (Sodium Chloride 0.9%, Glucose-saline combinations, Glucose 5%) but not Sodium Lactate Compound (Hartmann's) Infusion or Sodium Chloride Compound (Ringer's) Infusion (see Compatibility with Intravenous Infusions and Other Drugs above).

Overdosage

Overdosage with metronidazole appears to be associated with very few abnormal signs or symptoms. Disorientation and vomiting may occur, especially after ingestion of large amounts.

Presentation

Intravenous Infusion of Metronidazole BP, 500mg in 100mL, plastic Viaflex Minibag.

Packs of 10.

Shelf Life / Storage

The product has a shelf life of 2 years from the date of manufacture when stored in accordance with directions.

Store below 25°C, protect from light.

Medicine Classification

Prescription Medicine.

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