

Metronidazole

Metronidazole Intravenous Infusion BP 500mg/100mL

Presentation

Metronidazole 5mg/ml Infusion is a clear, colourless to pale yellow solution. Each mL contains metronidazole 5mg, together with sodium chloride, anhydrous disodium hydrogen phosphate, citric acid monohydrate and water for injections. The solution has a pH of between 4.5 and 6.0 with a calculated osmolarity of 310.8 mOsm/L.

Uses

Actions

Metronidazole, in common with tinidazole and nimorazole, is one of the nitroimidazole class of therapeutic agents and has activity against protozoa (Trichomonas, amoebae and Giardia lamblia) and anaerobic bacteria (including Bacteroides).

Metronidazole is reduced at the nitro group by intestinal bacteria, particularly anaerobes. A reactive intermediate is thereby formed which binds to critical sites in susceptible bacterial cells, with subsequent disruption of DNA and inhibition of its synthesis. Reduction is probably effected by low redox potential electron transport proteins which play a major role in the metabolism of anaerobes. The activity of metronidazole against Trichomonas, amoebae and Giardia is also likely to be attributable to disruption of existing DNA and inhibition of its synthesis in those organisms.

Pharmacokinetics

Absorption

Infusion: Peak plasma levels (mean of 18mcg/mL) of metronidazole occur at the end of infusion of 500mg over 20 minutes.

Distribution

Metronidazole is distributed widely through body tissues both intracellularly and extracellularly. It is found in saliva and breast milk in concentrations equivalent to those in serum. It also crosses the placenta and is found in the CSF. Therapeutic levels have been found in abscesses, bile, CSF, seminal fluid and in synovial fluid.

There is no significant plasma binding of metronidazole (less than 5%).

Metabolism and Excretion

Metronidazole is partly metabolised in the liver by both acid oxidation and glucuronic conjugation. Five metabolites of metronidazole have been identified in urine. These

include the hydroxy metabolite (1-(2-hydroxyethyl)-2-hydroxy- methyl-5-nitroimidazole) and the acid metabolite (1-acetic acid-2-methyl-5-nitroimidazole). The hydroxy metabolite has approximately 30% of the bioactivity of metronidazole against anaerobic bacteria whereas the acid metabolite has only 5% of the activity of unchanged metronidazole. About 15-20% of an administered dose is excreted in the urine as unchanged metronidazole. Overall, about 50-80% of an administered dose is excreted as nitro-containing compounds, of which unchanged metronidazole and the hydroxy-methyl analogue each account for about one third. The fate of the remainder of an administered dose is unknown.

Half-Life

The half-life of metronidazole after single, intravenous infusion has been reported as 7.3 ± 1.0 hours.

Metronidazole is also excreted into saliva and breast milk reaching concentrations equivalent to those in plasma.

Indications

Metronidazole intravenous infusion is indicated:

- For treatment of anaerobic infections in patients for whom oral administration is not possible.
- When immediate anti-anaerobic therapy is required.
- 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.

Dosage and Administration

A maximum of 4 g 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, eg. 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.

Contraindications

- Patients with evidence of a history of blood dyscrasias should not receive metronidazole since occasionally leukopenia has been observed during its administration.
- Active organic disease of the central nervous system.
- Pregnancy (first trimester) - see Use In Pregnancy.
- Hypersensitivity to metronidazole.

Warnings and Precautions

Long Term Therapy

For treatment over 10 days haematological tests are recommended. If abnormal neurological signs or leukopenia occurs metronidazole should be discontinued immediately.

Mutagenicity

Metronidazole has been found to be mutagenic in bacteria and some animal species. Reports of chromosomal aberrations have occurred after long periods and, in one incident, after 7 days treatment. While insufficient experimental evidence exists, the potential risk should be taken into account when prescribing metronidazole, especially in pregnancy.

Carcinogenicity

Tumorigenic activity has occurred in chronic oral administration of metronidazole in mice and rats, the most prominent being pulmonary lesions in the mouse.

All of the 5 mouse studies have shown this, including one study where the animals were dosed on an intermittent schedule (dosage during every 4th week only). One of the mouse studies indicated an increase in malignant lymphomas and pulmonary neoplasms associated with lifetime feeding of metronidazole.

Long term rat toxicity studies show a significant increase in various neoplasms, particularly mammary tumours. Two life-time tumorigenicity studies in hamsters have been reported to be negative.

Results of 771 women treated for *T. vaginalis* in a retrospective epidemiological study, failed to show any significant increase in cancer incidence. Risk of carcinogenicity emphasises the need to avoid indiscriminate use of metronidazole.

Animal Toxicity

The LD50 for dogs has been reported as 4.5g/kg. In mice and rats LD50 dosages have been reported in the range 1-5g/kg.

Cardiac Function Impairment

Care is required due to the sodium present (0.135 mmol/mL) in the injection.

Impaired Hepatic Function

As metronidazole is partly metabolised in the liver, caution should be exercised in patients with impaired liver function. Empirical dosage reduction and serum level monitoring may be necessary.

Impaired Renal Function

In patients on twice weekly haemodialysis, metronidazole and its major active metabolite are rapidly removed during an 8 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 hydroxy metabolite could be associated with side effects and

measurement of its plasma concentrations by high pressure liquid chromatography (HPLC) has been recommended.

While the pharmacokinetics of metronidazole are little changed in the presence of anuria, there is retention of the metabolites, the clinical significance of which is unknown.

Candidiasis

Candida overgrowth in the gastrointestinal or genital tract may occur during metronidazole therapy and may require treatment with an agent with activity against Candida.

Use during Pregnancy and Lactation

Category B2

Metronidazole should not be given in the first trimester of pregnancy as it crosses the placenta and enters foetal circulation rapidly. However, it has not been shown to be teratogenic in either human or animal studies.

It is recommended that the use for trichomoniasis in 2nd and 3rd trimester be restricted to those in whom local palliative treatment has been inadequate to control symptoms. In life threatening situations the risk/benefit ratio should be carefully considered.

Foetal alcohol syndrome, possibly due to acetaldehyde rather than alcohol, would prevent taking alcohol in association with metronidazole in pregnant women. Metronidazole inhibits aldehyde dehydrogenase, permitting accumulation of acetaldehyde (a breakdown product of ethanol).

Metronidazole is secreted in breast milk, the highest concentrations being 2 and 4 hours after administration, declining over the next 12 to 24 hours. Assuming tumorigenic and mutagenic potential of metronidazole, breastfeeding should be withheld for 12 to 24 hours after metronidazole administration thereby reducing the infant's exposure.

Adverse Effects

More Common Reactions

Dermatological: Rash, pruritis, urticaria.

Gastrointestinal: Nausea, anorexia, furry tongue, dry mouth, abdominal discomfort, glossitis, stomatitis (which may be associated with Candida overgrowth - see Precautions).

Nervous System: Metallic or unpleasant taste in the mouth, headaches, dizziness.

Less Common Reactions

Auditory and Vestibular: Vertigo, tinnitus.

Biochemical Abnormalities: Jaundice has been reported in one patient being treated for anaerobic infection. Altered renal function tests were noted in 2 patients on combined metronidazole and tobramycin therapy for intra-abdominal sepsis.

Cardiovascular: Flushing, flattening of the T wave, prolongation of the QT interval, thrombophlebitis.

Dermatological: Mild erythematous eruption.

Genito-Urinary: Darkening of urine (possibly due to a metabolite). Dysuria, dryness of vagina or vulva, cystitis, a sense of pelvic pressure, dyspareunia, polyuria, incontinence, decrease in libido, proctitis and pyuria have been reported during metronidazole therapy (although all of these may be attributable to the underlying pathology).

Musculoskeletal: Joint pains.

Respiratory: Nasal congestion.

Serious or Life Threatening Reactions: Leukopenia is usually transient and disappears on withdrawal of the medicine. If paraesthesia occurs, the drug should be discontinued and the symptoms usually disappear.

Gastrointestinal: Vomiting, diarrhoea, dyspepsia in patients with anaerobic infections. *Cl. difficile* colitis (one case).

Haematological and Reticulo-Endothelial: Leukopenia (usually moderate and transient - see Warnings and Precautions). One case of bone marrow aplasia attributable to metronidazole has been reported.

Nervous System: Lack of co-ordination, ataxia, convulsive seizures, confusion, irritability, depression, weakness, insomnia, disorientation, peripheral neuropathy, characterised mainly by numbness or paraesthesia of an extremity (see Warnings).

Interactions

Alcohol: Metronidazole taken in combination with alcohol may produce abdominal cramps, nausea, vomiting, headaches and flushing. The underlying mechanism and implications of this interaction are discussed under Use in Pregnancy.

Disulfiram: In a clinical trial of combined therapy with disulfiram and metronidazole in the treatment of chronic alcoholics, severe acute psychotic reactions occurred in 6 out of 29 patients.

Warfarin: Metronidazole inhibits the breakdown of the more potent S-isomer of warfarin. This is the pharmacologically active metabolite of the racemic parent molecule. Therefore, the activity of warfarin is enhanced by metronidazole.

Phenobarbitone: Decreases the effect of metronidazole probably due to increased metabolism.

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

Interference with Clinical Laboratory and Other Tests: Metronidazole may show negative interference with continuous flow spectrophotometry of aspartate aminotransferase (previously GOT) so that hepato-cellular damage which is detectable by raised serum AST may be missed.

NOTE: Caution should be exercised in patients receiving metronidazole I.V. and 40mmol potassium chloride injections concurrently as such combinations may be hypertonic.

Overdosage

Symptoms

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.

Treatment

Early gastric lavage is recommended, where metronidazole has been taken orally.

Pharmaceutical Precautions

Shelf life: 3 years from date of manufacture.

Protect from light. Store below 25°C.

Use within 7 days after removing infusion bag from the carton. Keep the infusion bag in the plastic overwrap until time of use.

Compatibility

Metronidazole infusion may be diluted to 1 in 5 or greater with appropriate volumes of normal saline, dextrose-saline, dextrose 5% w/v and with 20mmol and 40mmol potassium chloride injections. Additives should not be introduced into metronidazole IV solution. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion.

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 medicines should not be added directly to metronidazole infusion.

Medicines Classification

Prescription Medicine

Package Quantities

5 x PVC Infusion Bags containing Metronidazole 500mg in 100mL (0.5% w/v)

6 x PVC Infusion Bags containing Metronidazole 500mg in 100mL (0.5% w/v)

10 x PVC Infusion Bags containing Metronidazole 500mg in 100mL (0.5% w/v)

Further Information

Metronidazole is 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole.

Metronidazole intravenous infusion is an isotonic, ready-to-use solution, requiring no dilution or buffering prior to administration.

The total sodium content (derived from sodium chloride and anhydrous hydrogen phosphate) is 326.4 mg/100 ml per 500mg of metronidazole. This must be considered in patients on a restricted sodium intake when calculating total daily sodium intake.

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