METRONIDAZOLE

General Monograph,  
Antibacterial - Antiprotozoal

Pharmacology: Metronidazole is amebicidal, trichomonacidal and bactericidal. A chemically reactive, reduced form of metronidazole is thought to be responsible for the drug's activity. The reduced substrate affects anoxic or hypoxic cells causing loss of the helical structure of DNA, strand breakage and impairment of cellular function.

The spectrum of activity of metronidazole includes the following: Anaerobic gram-negative bacilli, including most Bacteroides species, Fusobacterium and Veillonella; anaerobic gram-positive cocci including Clostridium, Eubacterium, Peptococcus and Peptostreptococcus. Metronidazole is also active against H. pylori, G. vaginalis and the protozoa E. histolytica, T. vaginalis and G. lamblia. Metronidazole acts primarily against the trophozoite forms of E. histolytica and has limited activity against the encysted forms.

Metronidazole is not active against fungi, viruses and most other aerobic or facultative anaerobic bacteria, i.e., Actinomyces, Lactobacillus and P. acnes.

The mechanisms by which topical metronidazole reduces inflammatory lesions of rosacea are unknown.

Pharmacokinetics: Following oral administration, metronidazole is well absorbed from the gastrointestinal tract. Peak serum levels following an oral dose occur in 1 to 2 hours.

With normal usage, only trace amounts of metronidazole are found in the serum following topical application of a 0.75% gel to the skin. Following vaginal administration of a 5 g dose of a 0.75% gel, systemic absorption is minimal (equivalent to 2% of the mean serum concentration achieved following a single 500 mg oral dose). Metronidazole is less than 20% bound to serum proteins and is widely distributed in the body. It reaches all tissues and fluids, with CSF concentrations reaching approximately 43% of serum concentrations. The drug crosses the placenta and is distributed into breast milk. Metronidazole is metabolized in the liver. It is excreted primarily in the urine as metabolites, with 20% of a dose excreted as unchanged drug. The half-life of metronidazole in adults ranges between 6 and 12 hours. Accumulation may occur in patients with severely impaired hepatic function; dosage reduction may be indicated. Dosage adjustment is generally unnecessary in patients with decreased renal function.

Metronidazole is removed by hemodialysis but is not significantly removed by peritoneal dialysis.

Indications: Bacterial Infections: The treatment of serious infections caused by susceptible anaerobic bacteria, such as B. fragilis (and other species of Bacteroides), Clostridium, Fusobacterium, Peptococcus, and Peptostreptococcus species.

Metronidazole has been used orally in the treatment of antibiotic-induced diarrhea and colitis, including mild to moderate cases of pseudomembranous colitis caused by C. difficile.

In mixed aerobic and anaerobic infections, consideration should be given to the concomitant administration of an antibiotic appropriate for the treatment of the aerobic component of the infection (see Warnings).

Metronidazole is used in multiple-drug regimens for the treatment of H. pylori-associated peptic ulcer
Bacterial Vaginosis: The 1995 Canadian STD Guidelines recommended metronidazole for the treatment of this condition.

Periodontal Infections: Metronidazole is used in the treatment of periodontal infections. It is also used as an adjunct in the treatment of acute necrotizing ulcerative gingivitis (ANUG) caused by spirochetes, fusobacteria, and Bacteroides species.


Rosacea: For topical application in the treatment of inflammatory papules, pustules and erythema of rosacea.

**Contraindications:** Hypersensitivity to metronidazole or other nitroimidazole derivatives.

Metronidazole should not be administered to patients with active neurological disorders or a history of blood dyscrasia.

Warnings: Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria. In patients with mixed aerobic-anaerobic infections, appropriate concomitant antibiotics active against the aerobic component should be considered.

Convulsive seizures and peripheral neuropathy, characterized by numbness, tingling, pain, or weakness in the hands or feet, have been reported in patients treated with metronidazole (administered orally or i.v.). If abnormal neurologic symptoms occur, treatment must be discontinued immediately.

**Precautions:** When metronidazole is used in the treatment of trichomoniasis, sexual contacts should be treated concurrently regardless of symptomatology. To minimize the risk of reinfection and transmission, patients should be advised to abstain from intercourse or to use a condom during intercourse for the duration of treatment.

When metronidazole is used in the treatment of acute intestinal amebiasis and amebic liver abscess caused by E. histolytica, sequential treatment with an intraluminal amebicide (such as iodoquinol or paromomycin) is recommended. Metronidazole is not indicated in cases of asymptomatic amebiasis, as it has limited activity against encysted E. histolytica.

Transient eosinophilia and leukopenia have been observed during treatment with metronidazole.

Studies using chronic, oral administration of metronidazole in rats and mice have shown it to be carcinogenic and tumorigenic. Metronidazole has not been shown to be carcinogenic or tumorigenic in humans.

Treatment with metronidazole should be discontinued if ataxia or any other symptom of CNS involvement occurs.

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

**Drug Interactions:** Alcohol: Patients taking metronidazole should be warned against consuming alcohol (during therapy and for 24 hours post-treatment) because of a possible disulfiram-like reaction.
Anticoagulants: Metronidazole has been reported to potentiate the anticoagulant effect of warfarin resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy.

Barbiturates: metronidazole metabolism may be enhanced causing reduced serum concentrations.

Disulfiram: Administering disulfiram and metronidazole together may result in confusion and psychiatric reactions because of combined toxicity.

Lithium: Initiation of metronidazole therapy has been associated with increased serum lithium levels and, in a few cases, signs of lithium toxicity.

Pregnancy: Metronidazole crosses the placental barrier. Metronidazole should be withheld during the first trimester. In addition, it is advisable that administration be avoided during the second and third trimesters; however, if metronidazole treatment is considered necessary, its use requires that the potential benefits be weighed against the possible risks.

Lactation: Metronidazole is distributed into milk. Any unnecessary exposure to metronidazole should be avoided. If a nursing mother is treated with metronidazole, the breast milk should be expressed and discarded during treatment. Breast-feeding can be resumed 24 to 48 hours after treatment.

Children: Controlled studies in children are limited.

**Adverse Effects:** Cardiovascular: palpitation and chest pain.

CNS: peripheral neuropathy, convulsive seizures, transient ataxia, dizziness, drowsiness, confusion, insomnia and headache.

Peripheral neuropathies have been reported in a few patients receiving prolonged treatment with large doses of metronidazole. It would appear that the occurrence is not directly related to the daily dosage and that an important predisposing factor is the continuation of oral and/or i.v. medication for several weeks or months.

Profound neurological deterioration, within 2 hours after metronidazole administration, has been reported. The occurrence is not directly related to the dose.

Dermatologic: rash and pruritus. With topical use: dry skin, skin irritation, stinging or burning of the skin.

Gastrointestinal: diarrhea, nausea, vomiting, unpleasant metallic taste, anorexia, epigastric distress, dyspepsia, constipation, antibiotic-associated pseudomembranous colitis, dry mouth, glossitis, stomatitis, candidiasis (oral).

Genitourinary: dysuria, proliferation of C. albicans in the vagina, vaginal dryness and burning. Darkening of urine has been reported; this is probably due to a metabolite of metronidazole and has no clinical significance. With vaginal administration: burning or increased frequency of urination, vulvitis, burning or irritation of penis of sexual partner.

Hematologic: transient eosinophilia or leukopenia.

Hypersensitivity: Erythematous rash, urticaria, serum sickness-like reactions have been reported rarely.
Local Reactions: Thrombophlebitis has occurred with i.v. administration.

Metabolic: Gynecomastia has been reported rarely.

**Overdose:** Symptoms: Severe toxicity following overdosage with metronidazole is uncommon. Massive ingestion may cause vomiting, nausea, anorexia and headache. Insomnia, drowsiness, depression and darkening of urine may also occur.

Treatment: REG>There is no specific antidote. Symptomatic and supportive therapy is usually sufficient.

Dosage: Metronidazole is available as: an injection; oral capsules and tablets; vaginal gel, cream and inserts; topical cream or gel.

Anaerobic Infections: Duration of therapy depends upon clinical and bacteriological assessment. Treatment for 7 days should be satisfactory for most infections. However, in cases where infection sites cannot be drained or which are liable to endogenous recontamination by anaerobic pathogens, longer treatment may be required.

Adults: Oral: 500 mg every 8 hours (7.5 mg/kg every 6 to 8 hours), to a maximum of 4 g/24 hours.

I.V.: 500 mg by i.v. infusion every 8 hours (7.5 mg/kg every 6 to 8 hours), to a maximum of 4 g/24 hours. The injection should be infused i.v. at the rate of 5 mL/minute.

Children: 30 mg/kg/day i.v. in 3 divided doses or 15 to 30 mg/kg/day orally in 3 to 4 divided doses.

Antibiotic-associated Pseudomembranous Colitis: Adults: Doses of 750 mg to 2 g daily given in 3 or 4 divided doses for 7 to 14 days have been used.

*H. pylori*-associated Peptic Ulcer Disease: Adults: metronidazole 500 mg orally twice daily for 7 days together with a proton pump inhibitor and clarithromycin. Alternate regimens include metronidazole 250 mg orally 4 times daily for 7 days together with a proton pump inhibitor, bismuth subsalicylate and tetracycline.

Bacterial Vaginosis: The Canadian STD Guidelines 1995 recommend in adults a dose of 500 mg orally twice daily for 7 days. Alternatively, metronidazole gel 0.75%, one applicatorful intravaginally twice daily for 5 days or metronidazole 2 g orally in a single dose can be used. Routine treatment of male sexual partners is not necessary.

Trichomoniasis: The Canadian STD Guidelines 1995 recommend all cases and their sexual contacts should be treated regardless of symptoms. In adults, metronidazole 2 g orally as a single dose is recommended.

Alternate regimens include 250 mg orally 3 times daily for 7 days or 500 mg twice daily for 5 days.

Children: 15 to 20 mg/kg/day orally in 3 divided doses (maximum 250 mg 3 times daily) for 7 days or 40 mg/kg (maximum 2 g) in a single dose.

Amebiasis: Adults: Acute intestinal amebiasis or amebic hepatic abscess: 750 mg 3 times daily for 10 days. Treatment should be followed with a course of a luminal amebicide (see Precautions).

Children: 35 to 50 mg/kg/day in 3 divided doses for 10 days.
Giardiasis: Adults: 2 g daily for 3 days (preferably given at bedtime with food). Alternatively, 250 mg 3 times daily for 5 to 7 days.

Children: 15 mg/kg/day in 3 divided doses for 5 to 7 days. Alternatively, single daily dose treatment has been used, as follows: <25 kg: 35 mg/kg once daily for 3 days; 25 to 40 kg: 50 mg/kg once daily for 3 days (preferably given at bedtime with food); >40 kg: adult dose is given.

Periodontal Infections: The usual oral dose is 250 mg 3 times daily for 3 to 5 days. For severe infections, the oral dose is 500 mg twice daily for 3 to 5 days. As an adjunct in ANUG the usual oral dose is 250 mg 3 times daily for 3 to 5 days or for 7 to 10 days in more severe disease.

Rosacea: Topical metronidazole is applied to the affected areas twice daily, morning and evening, for 9 weeks.