Metronidazole exhibits in vitro minimum inhibitory concentration (MIC) of 8 mcg/mL or less against most strains (>90%) of gram negative and gram positive anaerobes. Metronidazole is active against most obligate anaerobes, but does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

Pharmacokinetics

Metronidazole is rapidly and almost completely absorbed after oral administration; bioavailability is 90 to 100%. Peak plasma concentrations (Cmax) of approximately 5 mcg/mL and 10 mcg/mL are achieved at an average of 1 to 2 hours after single oral doses of 250 mg and 500 mg, respectively. Some accumulation and consequently higher concentrations occur when multiple doses are given. Absorption may be delayed, but is not reduced overall, by administration of food. On a regimen of 500 mg three times daily administered by the intravenous (IV) route, a steady state was achieved after approximately three days. Comparison of the pharmacokinetics of oral and IV metronidazole showed that the area under the plasma metronidazole concentration (AUC) against time curves were essentially identical.

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 breastfeeding mothers in concentrations equivalent to those found in the plasma. It attains therapeutic concentrations in the bile and the cerebrospinal fluid (CSF). No more than 20% is bound to plasma proteins.

An oral or IV dose of metronidazole is partially metabolized in the liver by hydroxylation, acid side-chain oxidation and glucuronide conjugation. The major metabolite, 2-hydroxymethyl metronidazole, has some antiprotozoal activity in vitro. The plasma elimination half-life of an oral metronidazole is about 6 to 9 hours; that of the hydroxyl metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease. The biological half-life of a single intravenously administered dose of metronidazole has been determined as 7.3 hours + 1 hour.

The majority of metronidazole dose is excreted in the urine, mainly as metabolites; a small amount appears in the feces. Urine may be dark or reddish brown in color following oral and IV administration of the drug due to the presence of water-soluble pigments, which result from its metabolism.

Special Population:

Renal Impairment:

Subjects with end-stage renal disease (ESRD) (CLCR=8.1 + 9.1 mL/min) who received a single 500 mg IV infusion of metronidazole had no significant change in metronidazole pharmacokinetics but had 2-fold higher Cmax of hydroxyl-metronidazole and 5-fold higher Cmax of metronidazole acetate, compared to healthy subjects with normal renal function (CLCR=126 + 16 mL/min). Monitoring for metronidazole associated adverse events is recommended in ESRD patients due to accumulation of metronidazole metabolites.

Following a single 500 mg IV infusion or oral dose of metronidazole, the clearance of metronidazole was studied in ESRD patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A hemodialysis session lasting for 4 to 8 hours removed 40% to 65% of the administered metronidazole dose, depending on the type of dialyzer membrane used and the duration of the dialysis session. Supplementation of metronidazole dose following hemodialysis should be considered if the administration of metronidazole cannot be separated from the dialysis session. A peritoneal dialysis session lasting for 7.5 hours removed approximately 10% of the administered metronidazole dose.

Hepatic Impairment:

After a single 500 mg IV infusion of metronidazole, the mean AUC24 of metronidazole was higher by 114% in patients with severe (Child-Pugh C) hepatic impairment, and by 54% and 53% in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to healthy subjects. There were no significant changes in the AUC24 of hydroxyl-metronidazole in these patients. In patients with severe (Child-Pugh C) hepatic impairment, a reduction in metronidazole dose by 50% is recommended. No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Monitoring for metronidazole associated adverse events is recommended in patients with mild to moderate hepatic impairment.

Geriatric:

After a single 500 mg oral or IV dose of metronidazole, subjects >70 years old with no apparent renal or hepatic dysfunction had a 40% to 80% higher mean AUC of hydroxy-metronidazole, with no apparent increase in the mean AUC of metronidazole, compared to young healthy subjects. Monitoring for metronidazole associated adverse events is recommended.

Pediatrics:

Newborn infants showed 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 between 28 and 40 weeks, the corresponding elimination half-lives ranged from 10.9 to 22.5 hours.