PRESCRIBING INFORMATION

METRONIDAZOLE

Metronidazole Oral Capsules

500 mg

Metronidazole Tablets

250 mg

ANTIBACTERIAL - ANTIPROTOZOAL

AA PHARMA INC.
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DATE OF REVISION:
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PRESCRIBING INFORMATION

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500 mg

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THERAPEUTIC CLASSIFICATION

Antibacterial - Antiprotozoal

ACTIONS AND CLINICAL PHARMACOLOGY

Metronidazole is bactericidal against anaerobic bacteria, it exerts trichomonacidal activity and is also active against *Giardia lamblia* and *Entamoeba histolytica*. Its exact mechanism of action has not been entirely determined as yet. It has been proposed that an intermediate in the reduction of metronidazole, produced only in anaerobic bacteria and protozoa is bound to deoxyribonucleic acid and electron-transport proteins, inhibits subsequent nucleic acid synthesis.

At present, the mechanism by which topical metronidazole reduces the lesions and erythema associated with acne rosacea is not precisely known. Despite the established anti-microbial effects of metronidazole, there is no evidence that the suppression of bacteria or parasitic mites harbored in the skin is directly responsible for its beneficial effects in rosacea. In vitro and in vivo studies indicate that metronidazole has direct anti-inflammatory activity and affects neutrophil chemotaxis and cell-mediated immunity. An antioxidant action via inhibition of neutrophil-generated reactive oxygen species has also been demonstrated; this action is believed to underlie its anti-inflammatory effect. It has been proposed that the reduction in rosacea lesions and erythema is the result of anti-inflammatory or immunosuppressive actions of metronidazole.

Clinical Pharmacokinetics

Human: Following oral administration, metronidazole is completely absorbed with plasma concentration usually reaching a peak within 1 to 2 hours. After single oral 500 mg doses, peak plasma levels of approximately 13 mg/L were obtained. On a regimen of 500 mg t.i.d. administered by the i.v. route, a steady state was achieved after approximately three days. The mean peak and trough concentrations measured at that time were 26 and 12 mg/L respectively, and the elimination half-life was approximately 7 to 8 hours. Comparison of the pharmacokinetics of oral and i.v. metronidazole revealed that the area under the plasma metronidazole concentration against time curves were essentially identical.

There is negligible percutaneous absorption following topical application of metronidazole 1% cream. In healthy volunteers who applied a single 100 mg dose of 14C-labelled metronidazole 2% cream to intact skin, no metronidazole could be detected in plasma after 12 hours. Only about 1% and 0.1% of the applied dose could be found in urine and feces, respectively. After once-daily application of the 1% cream for 1 month, only traces (about 1% of the C_{max} of a 200 mg oral dose) could be detected in 25% of patients. In the rest of the patients, no detectable plasma levels were found.

Excretion and Metabolism

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose) with fecal excretion accounting for 6 to 15% of the dose. The metabolites that appear in the urine result primarily from side chain oxidation (i.e. 1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5 nitroimidazole-1-yl-acetic acid) and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total.

Metronidazole is the major component appearing in the plasma with lesser quantities of the 2-hydroxymethyl metabolite also being present. The ratio of these components varies with time but the maximum concentration of the metabolite (C_{max}) is approximately 20% of the C_{max} of metronidazole for the oral route of administration.

Protein Binding

Less than 20% of the circulating metronidazole is bound to plasma proteins.

Tissue distribution

The concentrations of metronidazole found in various tissues and body fluids are given in the following table:

TISSUE OR FLUID	DOSE ADMINISTRATION	TISSUE OR FLUID LEVEL	PLASMA LEVEL
Bile	500 mg q.i.d. p.o. x 10 days	26 mg/L (on day 5) 20 mg/L (on day 15)	N/A* N/A
Saliva	500 mg p.o. single dose	7 mg/L (at 2-3 hour)	N/A
Placenta	250 mg p.o. single dose	0 to 1.4 mg/kg (at 4-5 hour)	3.0 – 6.9 mg/L (maternal)
Embryo	250 mg p.o. single dose	0 to 1.0 mg/kg	3.0 – 6.9 mg/L (maternal)
Breast Milk	200 mg p.o.	1.3 to 3.4 mg/L	1.8 – 3.9 mg/L
Cerebrospinal fluid	500 mg p.o. b.i.d.	11.0 to 13.9 mg/L	8.3 – 15.4 mg/L
Pus (brain abscess)	400 mg p.o. t.i.d. 600 mg p.o. t.i.d.	35 mg/L inflamed meninges 43 mg/L	N/A N/A
Pus (pulmonary empyema)	400 mg p.o. q.i.d.	24.2 mg/L	N/A

*Not available

Decreased Renal Function

Decreased renal function does not appear to alter the single dose pharmacokinetics of metronidazole, although the elimination half-life of the metabolites is prolonged.

Haemodialysis

During haemodialysis, the hydroxy metabolite is removed from the plasma about three times more rapidly than in normal subjects. Comparison of the elimination half-lives of metronidazole and two metabolites are given in the following table.

METRONIDAZOLE ELIMINATION IN NORMAL SUBJECTS AND IN PATIENTS WITH RENAL INSUFFICIENCY FOLLOWING A SINGLE INTRAVENOUS DOSE OF METRONIDAZOLE (500 MG)

	ELIMINATION HALF LIFE (hours)		
		Patients	
Compound	Normal Subjects	on dialysis	between dialysis
Metronidazole	7.3 ± 1.0	2.6 ± 0.7	7.2 ± 2.4
1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole	9.8 ± 1.3	7.8 ± 4.1	34 ± 43
2-methyl-5 nitroimidazole-1-yl-acetic acid	—	7.9 ± 4.1	138 ± 82

Therefore, no accumulation should occur in anuric patients undergoing regular dialysis.

Continuous Ambulatory Peritoneal Dialysis

Metronidazole was given I.V. at 750 mg to five patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Insignificant changes were noted in the pharmacokinetic parameters

of metronidazole (apparent volume of distribution, elimination half-life, total body clearance). Peritoneal dialysis does not appear to reduce the serum levels of metronidazole metabolites.

Impaired Liver Function

In patients with impaired liver function, the plasma clearance of metronidazole is decreased and accumulation can therefore result.

Animal: Metronidazole exerted no central nervous system activity except at very high doses. At doses of 0.5g/kg and above, some anticonvulsant activity was demonstrated in mice and rats, spinal reflexes were inhibited in the anaesthetised cat and hypnosis was produced in the rat.

Metronidazole at doses of 40 to 50 mg/kg administered by intravenous infusion to 4 anaesthetised dogs produced a slight fall in blood pressure and heart rate for 30 to 60 minutes after the infusion. There was little or no effect on the electrocardiographic tracings. With both metronidazole and the vehicle, there was a tendency for dogs to bleed more readily than untreated animals although plasma prothrombin times remained within normal limits.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy male volunteers. The rate and extent of absorption of metronidazole was measured, and compared following oral administration of a single 1 x 500 mg dose of METRONIDAZOLE (Metronidazole Oral Capsules), and Flagyl® (metronidazole) capsules, under fasting conditions. The results from measured data are summarized below.

Summary Table of the Comparative Bioavailability Data Metronidazole (Dose: 1 x 500 mg) From Measured Data - Under Fasting Conditions Based on Metronidazole				
Parameter	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
	Metronidazole	Flagyl®†		
AUC_T (ng.h/mL)	120859 121913 (14)	121439 122428 (13)	99.5	97.5 – 101.6
AUC_I (ng.h/mL)	123300 124503 (15)	123863 125005 (14)	99.5	97.5 – 101.6
C_{MAX} (ng/mL)	10950 11148 (22)	11187 11403 (22)	97.9	93.2 – 102.8
T_{MAX}^{*} (h)	1.27 (56)	1.41 (64)		
$T_{½}^{*}$ (h)	8.37 (13)	8.27 (15)		

* Arithmetic means (CV%).

** Based on the least squares estimate.

† Flagyl® by Rhône-Poulenc Rorer, purchased in Canada.

INDICATIONS AND CLINICAL USE

Bacterial Infections

Treatment: Culture and susceptibility studies should be performed to determine the causative organisms and their susceptibility to metronidazole. Based on clinical judgment and anticipated bacteriological findings, therapy may be started while awaiting the results of these tests. However, modification of the treatment may be necessary once these results become available.

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 has also been used in the treatment of a small number of cases of brain or lung infections (some with abscesses) caused by anaerobic bacteria.

Prophylaxis: If there are signs of infections, specimens for culture should be obtained for the identification of causative organisms so that appropriate therapy may be given.

Bacterial Vaginosis

The "1988 Canadian Guidelines for the Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults" recommends metronidazole for the treatment of this condition.

Protozoal Infections

– Trichomonal infections in men as well as in women.

– Hepatic and intestinal amebiasis.

– Giardiasis.

CONTRAINDICATIONS

METRONIDAZOLE (metronidazole) is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

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

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.

Known or previously unrecognized moniliasis may present more prominent symptoms after treatment with metronidazole.

Studies in rats and mice have provided some evidence that metronidazole may cause tumors in these species when administered orally for a long period at high doses. The relevance of these findings in humans is not known. However, it is therefore recommended that in the treatment of trichomoniasis, the use of metronidazole should be confined to those patients in whom significant T. vaginalis infection has been confirmed by appropriate diagnostic techniques.

Severe neurological disturbances (i.e. convulsive seizures and peripheral neuropathy) have been reported in patients treated with metronidazole. These have been observed very infrequently.

Patients should be warned about the potential for confusion, dizziness, hallucinations or convulsions, and advised not to drive or operate machinery if these symptoms occur.

PRECAUTIONS

General

Where there is clinical evidence of a trichomonal infection in the sexual partner, he should be treated concomitantly to avoid reinfection.

A rare case of reversible but profound neurological deterioration has been reported following a single oral dose of metronidazole; it is therefore advisable that a patient taking metronidazole for the first time not be left unattended for a period of two hours. The appearance of abnormal neurologic signs demands prompt discontinuation of Metronidazole therapy and, when severe, immediate medical attention. Gastric lavage may be considered if no more than two or three hours have elapsed since administration of the drug.

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.

Treatment with metronidazole should be discontinued should pancreatitis occur once other causes of this disease are excluded.

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering metronidazole Injection to patients receiving corticosteroids or to those predisposed to edema.

Hematologic

Transient eosinophilia and leukopenia have been observed during treatment with metronidazole. Regular total and differential leukocyte counts are advised if administration for more than 10 days or a second course of therapy is considered to be necessary.

Pregnancy

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Although metronidazole has been given to pregnant women without apparent complication, it is advisable that administration of metronidazole be avoided in pregnant patients and be withheld during the first trimester of pregnancy. In serious anaerobic infections, if the administration of metronidazole to pregnant patients is considered to be necessary, its use requires that the potential benefits to the mother be weighed against the possible risks to the fetus.

Nursing mothers

Metronidazole is secreted in breast milk in concentrations similar to those found in plasma. Administration of metronidazole should be avoided in the nursing mother.

Children

Clinical experience in children is very limited. The monitoring of this group of patients is particularly important. The safety and effectiveness of intravenous metronidazole in children has not been established.

Laboratory Test Interferences

Metronidazole interferes with serum AST (SGOT), ALT (SGPT), LDH, triglycerides and hexokinase glucose determinations which are based on the decrease in ultraviolet absorbance which occurs when NADH is oxidized to NAD. Metronidazole causes an increase in absorbance at the peak of NADH (340 nm) resulting in falsely decreased values.

Drug Interactions

Patients taking metronidazole should be warned against consuming alcohol during therapy and for at least one day afterwards, because of the possibility of a disulfiram-like reaction. This reaction appears to be due to-the inhibition of the oxidation of acetaldehyde, the primary metabolite of alcohol.

Administration of disulfiram and metronidazole has been associated with acute psychoses and confusion in some patients; therefore, these drugs should not be used concomitantly.

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.

In single dose studies, metronidazole injection did not interfere with the biotransformation of diazepam, antipyrine or phenytoin in man. However, patients maintained on phenytoin were found to have toxic blood levels after oral metronidazole administration. Phenytoin concentration returned to therapeutic blood level after discontinuance of metronidazole.

The metabolism of metronidazole has been reported to be increased by concurrent administration of phenobarbital. It is recommended that increased doses of metronidazole Injection be considered in such cases.

A slight potentiation of the neuromuscular blocking activity of vecuronium has been reported in patients administered metronidazole at a dose of 15 mg/kg.

Concomitant use of lithium and metronidazole may result in lithium intoxication due to decreased renal clearance of lithium. Persistent renal damage may develop. When metronidazole must be administered to patients on lithium therapy, it may be prudent to consider tapering or discontinuing lithium temporarily when feasible. Otherwise frequent monitoring of lithium, creatinine and electrolyte levels and urine osmolality should be done.

Metronidazole has been reported to reduce the clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.

ADVERSE REACTIONS

Gastrointestinal: diarrhea, nausea, vomiting, anorexia, epigastric distress, dyspepsia, constipation, and rare cases of pseudomembranous colitis. Reversible cases of pancreatitis have been reported infrequently.

Mouth: furred tongue, dry mouth, unpleasant metallic taste, glossitis.

Liver: very rare cases of reversible abnormal function tests and cholestatic hepatitis have been reported.

Haematopoietic: transient eosinophilia, leukopenia, very rare cases of agranulocytosis and thrombocytopenia have been reported.

Dermatologic: rash and pruritus.

Hypersensitivity reactions: flushing, urticaria, fever, angioedema, exceptional anaphylactic shocks.

Cardiovascular: palpitation and chest pain.

Central Nervous System: convulsive seizures, peripheral neuropathy, transient ataxia, dizziness, drowsiness, insomnia, headache and psychiatric disorders, such as confusion and hallucinations.

Peripheral neuropathies have been reported in a few patients on moderately high to high-dose prolonged oral treatment with 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 dosage level.

Metabolic: An antithyroid effect has been reported by some investigators but three different clinical studies failed to confirm this.

Local Reactions: Thrombophlebitis has occurred with I.V. administration.

Other: Proliferation of *Candida albicans* in the vagina, vaginal dryness and burning; dysuria; occasional flushing and headaches, especially with concomitant ingestion of alcohol; altered taste of alcoholic beverages.

Darkening of the urine has been reported. This is probably due to a metabolite of metronidazole and seems to have no clinical significance. Reversible lowering of serum lipids has been reported.

A single case of gynecomastia has been reported which resolved on discontinuing metronidazole administration.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptom

Single oral doses of metronidazole, up to 12 g have been reported in accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. Neurotoxic effects, including seizures and peripheral neuropathy have been reported after 5 to 7 days of oral doses of 6 to 10.4 g every other day.

Treatment

There is no specific antidote. Early gastric lavage may remove a large amount of the drug; otherwise, symptomatic treatment.

DOSAGE AND ADMINISTRATION

ANAEROBIC INFECTIONS

Adults

Treatment

TREATMENT SHOULD BE INITIATED BY THE I.V. ROUTE. Oral medication may be substituted when it is feasible and/or practical.

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

Oral Administration

500 mg every 8 hours.

Severe hepatic disease: Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites. Accordingly, doses below those usually recommended should be administered and with caution. However, due to a lack of pharmacokinetic information, specific dosage recommendations cannot be given for these patients. Therefore, close monitoring of blood metronidazole levels and of the patients for signs of toxicity are recommended (see WARNINGS and PRECAUTIONS).

Severe impairment of renal function and anuria: The elimination half-life of metronidazole in anuric patients is not significantly altered. However, the elimination half-lives of the metabolites of metronidazole are significantly increased (3- to 13-fold). Consequently, although metronidazole would not be expected to accumulate in these patients, accumulation of the metabolites would be expected. The potential for toxicity of these metabolites is not known.

Patients on hemodialysis: The dose of metronidazole need not be specifically reduced since accumulated metabolites may be rapidly removed by hemodialysis.

Patients on peritoneal dialysis: Peritoneal dialysis does not appear to reduce serum levels of metronidazole metabolites.

Patients with severe impairment of renal function who are not undergoing hemodialysis should be monitored closely for signs of toxicity.

Children: The safety and effectiveness of metronidazole in children is not known. Due to lack of pharmacokinetic data, no dosage recommendations can be made (see PRECAUTIONS).

TREATMENT OF BACTERIAL VAGINOSIS

Adults

500 mg orally twice a day for 7 days.

Concurrent treatment of sexual partners is not usually indicated.

TREATMENT OF TRICHOMONIASIS

Consideration should be given to use metronidazole therapy (oral or vaginal) in female patients, only when trichomonal infection has been confirmed by appropriate diagnostic techniques. In the male patient, oral metronidazole is recommended in those who are evidently the source of reinfection in female consorts and those with demonstrated urogenital trichomoniasis (see WARNING section).

Oral Administration

Single-Dose Treatment: For both women and men, 2g administered as a single dose after a meal.

Standard Ten-day Treatment: Women - One 250 mg tablet twice a day, morning and night for 10 consecutive days. Men - One 250 mg tablet twice a day for 10 consecutive days.

For both men and women, it may be occasionally necessary to give a second ten-day course after 4 to 6 weeks.

TREATMENT OF AMEBIASIS

Adults

Intestinal Amebiasis - Three 250 mg tablets (750 mg) three times daily for 5 to 7 days.

Amebic abscesses of the liver - Two to three 250 mg tablets (500 to 750 mg) three times daily for 5 to 7 days.

Children

Administer 35 to 50 mg/kg/day in three divided doses for 5 to 7 days.

TREATMENT OF GIARDIASIS

Adults

One 250 mg tablet twice daily for 5 to 7 days.

Children

Administer 25 to 35 mg/kg/day in two divided doses for 5 to 7 days.

Note: The efficacy of the recommended dosages for the treatment of amebiasis and giardiasis has been demonstrated. However, the optimal dose, the duration of treatment and the risk of recurrence have not been completely established.

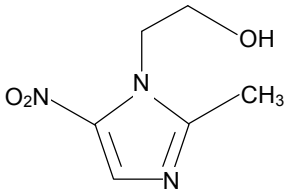
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Metronidazole

Chemical Name: 2-methyl-5-nitroimidazole-1-ethanol

Structural Formula:



Molecular Formula: $C_6H_9O_3N_3$

Molecular Weight: 171.15

Physical Form: White crystalline powder with slight yellow tint.

Solubility: Slightly soluble in water, alcohol, chloroform and ether.

pka: 2.6

pH: 5.8

Melting Point: 159-163°C

Composition

Capsules: In addition to the active ingredient (metronidazole) each METRONIDAZOLE (Metronidazole Oral Capsule), 500 mg contains the non-medicinal ingredients: croscarmellose sodium, colloidal silicon dioxide and stearic acid. The capsule shell contains the following non-

medicinal ingredients: gelatin, D&C red #33, D&C yellow #10, FD&C blue #1, FD&C green #3, talc (antistatic agent) and titanium dioxide. The edible ink used to imprint the capsule shells contains the following non-medicinal ingredients: black iron oxide, shellac glaze, propylene glycol, FD&C blue #2, and FD&C red #40.

Tablets: In addition to the active ingredient (metronidazole) each METRONIDAZOLE (Metronidazole Tablet), 250 mg contains the non medicinal ingredients: croscarmellose sodium, colloidal silicon dioxide, microcrystalline cellulose and magnesium stearate.

Stability and Storage Recommendations

METRONIDAZOLE (Metronidazole Oral Capsules) and METRONIDAZOLE (Metronidazole Tablets) should be stored at 15 to 25°C.

AVAILABILITY OF DOSAGE FORMS

METRONIDAZOLE (Metronidazole Oral Capsules), 500 mg: Each pale green and light grey capsule, printed "500" contains 500 mg of metronidazole. Available in bottles of100 capsules.

METRONIDAZOLE (Metronidazole Tablets), 250 mg: Each round, white biconvex, film coated, engraved "250"one one side and plain on the other, contains 250 mg of metronidazole. Available in bottles of100 and 500 tablets.

MICROBIOLOGY

BACTERIOLOGY

Metronidazole is active in vitro against most obligate anaerobes but does not appear to possess any relevant clinical activity against facultative anaerobes or obligate aerobes.

In one study the minimum inhibitory concentrations of metronidazole were determined in 730 strains of anaerobic bacteria isolated from clinical specimens. The results are summarized in the following table:

ACTIVITY* OF METRONIDAZOLE AGAINST ANAEROBIC BACTERIA

BACTERIA	No of strains tested	CUMULATIVER PER CENT SUSCEPTIBLE AT THE INDICATED CONCENTRATION (mg/mL)										
		0.1	0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0	128	256
Bacteroides fragilis group	77	1	12	27	56	84	97	99	100			
Bacteroides melaninogenicus	69	15	81	93	99	100						
Other bacteroides	72	6	42	68	85	93	96	96	99			100
Fusobacterium nucleatum	19	58	95			100						
Other fusobacterium	46	15	76	100								
Peptococcus and Gaffkya	73	3	69	88	96						96	100
Peptostreptococcus	41	29	66	76	81	83	88	90				100
Microaerophilic and anaerobic streptococci	11		27			36					46	100
Gram-negative cocci (Acidaminococcus, Megashaera, Veillonella)	28	4	57	89	96	100						
Eubacterium	59	7	44	61	66		71		75	80	86	100
Arachnia	3		33									100
Propionibacterium	12		8			17						100
Actinomyces	16					13		19	50	56	63	100
Bifidobacterium	8					36		66	75	87		100
Lactobacillus	20	10	35	55		65	75			80	90	100
Clostridium perfringens	12		25	67	100							
Other clostridium	164	32	54	65	74	84	93	98	100			

*Determined using an agar dilution technique described in the Wadsworth Anaerobic Bacteriology Manual 2nd Ed. University of California, Los Angeles, Extension Division, 1975.

With rare exceptions, anaerobic gram-negative non-spore forming bacilli and cocci as well as Clostridium species were susceptible to concentrations of metronidazole of 16 mg/L or less. A few strains of Peptococcus and Peptostreptococcus required 128 mg or more per litre of metronidazole for inhibition. Metronidazole was relatively ineffective against Streptococcus strains and the gram-positive non-spore forming bacilli.

A series of in vitro determinations demonstrated that the minimum bactericidal concentrations against susceptible strains are generally within one dilution of the minimum inhibitory concentrations.

With Bacteroides fragilis 10^3 fold increases in inoculum size have resulted in two to four fold increases in M.I.C. and M.B.C. values. The bactericidal effect of metronidazole is not significantly affected by pH changes within the range of 5.5 to 8.0.

Susceptibility testing

Quantitative methods give the most precise estimate of susceptibility to antibacterial drugs. A standardized agar dilution method and a broth microdilution method are recommended. A bacterial isolate may be considered susceptible if the M.I.C. value for metronidazole is not more than 16 mg/L. An organism is considered resistant if the M.I.C. is greater than 16 mg/L.

PARASITOLOGY

Trichomonacidal Activity

In Vitro activity was studied using decreasing concentrations of metronidazole which were added to a series of Trichomonas vaginalis cultures maintained at 37°C. A 1:400,000 dilution of metronidazole killed up to 99% of the trichomonads in 24 hours.

In Vivo, 0.5 mL of a 48-hour culture of Trichomonas vaginalis injected under the dorsal skin in a control and a test group of mice revealed, seven days later, extensive abscess-like lesions swarming with trichomonads in the control group and normal sub-cutaneous tissue free of trichomonads in the animals which had received oral metronidazole in a daily dosage of 12.5 mg/kg of body weight.

Amebicidal Activity

In Vitro: The minimum inhibitory concentration of metronidazole required to immobilize over a 48-hour period a culture of Entamoeba histolytica maintained at 37°C was 3 mg/L.

In Vivo: The amebicidal activity of metronidazole has been demonstrated in various tests.

In the young rat, an intestinal infestation was induced in the caecum by the inoculation of an amebic culture or of a homogenate of caecums obtained from young rats previously infested in the same manner. Metronidazole, 100 mg/kg/day p.o. administered during 4 consecutive days, the first dose being given 24 hours after infestation, protected all the animals. On the other hand, when the drug was administered on 4 consecutive days, starting on the day that the animals were infested, it had a CD_{50} of 22 mg/kg/day in the intestinal amebiasis of the young rat. Finally, the CD_{50} when the product was given in a single dose 24 hours after infestation was 49 mg/kg/day p.o.

In the hamster, hepatic amebiasis was induced by the inoculation of a culture of amebae under the capsule of Glisson; metronidazole administered orally during 4 consecutive days protected all the animals at a dosage of 35 mg/kg/day while its CD_{50} was 15 mg/kg/day.

Activity Against Giardiasis

The activity of metronidazole against giardiasis has been demonstrated in mice infested by *Lamblia muris*. The product administered once a day on two consecutive days had a CD_{50} of 30 mg/kg/day while its therapeutic index was 1/100.

TOXICOLOGY

Acute Toxicity

The LD_{50} values for metronidazole are given in the following Table:

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	—	p.o.	4350
	M	i.p.	3650
	M	i.v.	1170
	F	i.v.	1260
Rat	—	p.o.	5000
	M	i.p.	5000
	M	i.v.	1575
	F	i.v.	1575

Signs of toxicity following oral and intravenous administration of metronidazole were sedation, ataxia and death in mice, and sedation and death in rats.

The acute toxicity of metronidazole was also tested in dogs. Beagle dogs (male or female, 1 dog per dose) were administered single oral doses of 500, 750, 1000, 1500, 3000 or 5000 mg/kg of metronidazole by gastric intubation. The highest oral dosage which did not produce neurological disturbances and severe vomiting was 500 mg/kg. At the higher doses, ataxia, loss of spatial judgment, dozing, walking blindly, a general state of unawareness, convulsion, retching and/or

vomiting were observed. There were no deaths but the dogs which received 1500 and 5000 mg/kg were killed on humane grounds 48 and 2½ hours after dosing, respectively.

Pairs of one male and one female beagle were administered total doses of 125, 200 or 250 mg/kg of metronidazole. These were given as 4 or 5 separate injections at hourly intervals, except for the 125 mg/kg dose which was given at half-hourly intervals. At 200 mg/kg, the male trembled during the third injection, the female appeared slightly lethargic following the third injection and its heart rate was rapid during the final injection. Following the 125 mg/kg and 250 mg/kg doses, no sign nor evidence of intolerance at the injection sites was observed.

The ocular irritant effects of 0.5%, 1% and 2% topical metronidazole cream and placebo cream were tested in rabbits. An aliquot (0.1 mL) of one of the cream formulations was placed in the lower lid of one eye of each of three animals. The eyes were subsequently examined for the appearance and severity of ocular lesions after 1 hour, and 1, 2, 3, 4, and 7 days after instillation. Mild conjunctival irritation was noted in several animals in both the active and placebo cream groups. The eyes of the animals in all treatment groups normalized within 1 to 3 days of instillation. None of the rabbits showed any corneal or inidial inflammation.

Subacute And Chronic Toxicity

Rats were administered metronidazole orally at doses of 0, 25 and 50 mg/kg for a month, 100 mg/kg for fifteen days, and 1000 mg/kg for thirty days. Except for testicular changes which consisted of minor epithelial desquamation and fewer spermatocytes in the epididymus in the 100 and 1000 mg/kg groups, no other abnormalities were observed. No interference with fertility or embryogenesis was observed.

Twenty male and 20 female rats were administered metronidazole intravenously at a dose of 30 mg/kg/day for 4 weeks. There was no evidence of local intolerance at the injection site. A statistically significant decrease in body weight gain was noted in the males only, with their overall weight increase being about 90% that of controls. Mean absolute and relative (to bodyweight) thyroid weights were significantly lower (by approximately 25%) than the control values in both sexes in the treated group. However, at microscopic examination, the architecture of the thyroid glands of treated animals was within normal limits. In another study conducted under the same experimental conditions, assessment of the thyroid function before and at the end of the dosing period revealed no effect of metronidazole in rats.

Dogs were administered metronidazole orally at doses of 0, 25 and 50 mg/kg for a period of one month. They showed no physical or biological alteration and no tissue modification. Other dogs dosed at 75, 110 and 225 mg/kg for a period of six months developed ataxia, muscular rigidity and tremor. No apparent dulling of the sensorium was noted.

Two male and 2 female dogs were administered metronidazole intravenously at doses of 37.5 mg/kg 5 days per week for 4 weeks. In the two males and in one of the 2 females, the relative weights of the thyroids were below control values (31% decrease for males and 26% decrease for females).

Teratogenicity Studies

Metronidazole has been evaluated for its embryotoxic and teratogenic potential in the rat, rabbit and mouse. In four studies performed in the rabbit, the compound was administered orally by capsule, by buccal intubation or by gastric intubation at doses of 30 to 200 mg/kg/day for periods ranging from 3 to 13 days during pregnancy. Neither embryotoxic nor teratogenic effects related to drug administration were observed.

In one study metronidazole was administered intravenously to rabbits (18 per group) at doses of 15 or 30 mg/kg/day from days 6-18 of pregnancy inclusive. There were no statistically significant differences between control and treated groups for any foetal parameter, but discrepancies between the numbers of corpora lutea and implantation sites suggested that the drug may have caused a 10-15% increase in pre-implantation loss. No embryotoxic or teratogenic effects were observed.

In five rat studies, metronidazole was administered either at a dietary concentration of 0.13% for 18 days of gestation, or by gastric intubation at dose levels from 50 to 200 mg/kg/day for periods ranging from 10 days (mid-gestation) to 40 days (before and during pregnancy). Drug-related embryotoxic or teratogenic effects were not observed in any of the five studies.

In rats, metronidazole was administered intravenously at doses of 15 or 30 mg/kg/day from days 5-17 of pregnancy inclusive. There was a statistically significant increase in the mean numbers of implantations and live foetuses per litter in the metronidazole treated groups, but no difference in any other foetal parameter.

In one mouse study, two groups of mice were treated from the sixth to the fifteenth day of gestation. Metronidazole was administered by gastric intubation at doses of 10 and 20 mg/kg/day. At the dosage utilized, metronidazole was devoid of any teratogenic activity.

In humans, data has been accumulated on 2500 women who received Metronidazole at various stages during pregnancy. The overall incidence of congenital abnormalities remained within the expected limits for untreated mothers and an examination of the reports revealed that there was no trend or consistent pattern in the reported defects nor was there any evidence of causal relationship.

Mutagenicity Studies

The mutagenic potential of metronidazole has been measured in two test systems. In a study using a bacterial indicator strain to detect mutagenic effects, positive results were reported. The inherent antimicrobial property of metronidazole further complicates the interpretation respecting genetic and carcinogenic hazard to man. The other test system, the dominant lethal test, measured the effect of metronidazole on mammalian germ cells. Male rats administered doses of metronidazole up to 600 mg/kg/day for five consecutive days, were mated to untreated females. Fetal deaths, the primary measure of dominant lethality, were not increased in those females mated to treated males.

Tumorigenicity Studies

Two separate tumorigenic studies were carried out in two different strains of mice with metronidazole. Metronidazole was administered in the diet at daily doses of 75,150 and 600 mg/kg in both experiments.

A study with the strain of Swiss mice was terminated after 78 weeks, while the other experiment with CF_1 mice was terminated at 92 weeks.

There was no evidence that the administration of metronidazole at any dosage level produced an adverse effect upon the physical appearance, behavior, body weight and food consumption. However, the survival in mice in the treated groups was better than that in the controls.

Statistical analysis of necropsy data, gross and microscopic, using life-table and other techniques revealed a significant increase in the rate of benign lung tumors in the groups of mice treated with 600 mg/kg. With the lower dosage, there was also a trend for increased rate; however, the changes were not significant. It should, though, be noted that this type of tumor was also seen in up to 30% of mice in the untreated groups.

In the rat, dose levels of 75, 150 and 300 mg/kg/day were administered orally in the diet for 80 consecutive weeks; a dosage of 600 mg/kg was administered for 13 weeks only. No consistent deleterious effects were observed with doses of 75 and 150 mg/kg for 28-80 weeks on physical, behavioral, clinical laboratory or post-mortem examinations. At the dosage of 300 mg/kg, testicular dystrophy was regularly encountered at 13 weeks or longer and was not reversed by a 28 week recovery (no drug) period; prostatic atrophy was also seen at 26 weeks. The 600 mg/kg dosage group showed a high incidence of testicular dystrophy and prostatic atrophy with a pronounced reduction in the rate of body weight gain. There was a significant increase in the number of benign mammary tumors only in the females of the 300 mg/kg group.

Two independent tumorigenicity studies conducted in the hamster gave negative results.

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