PRODUCT MONOGRAPH

[Pr]RIFADIN®

Rifampin capsules USP
150 mg & 300 mg

Antibiotic

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Date of Revision:
July 23, 2010

Submission Control No.: 138653

s-a Version 4.0 dated July 23, 2010

PRODUCT MONOGRAPH

Pr RIFADIN®
(rifampin)

Capsules
150 mg & 300 mg

Antibiotic

CLINICAL PHARMACOLOGY

RIFADIN (rifampin) inhibits DNA-dependent RNA polymerase activity in susceptible cells. Specifically, it interacts with bacterial RNA polymerase, but does not inhibit the mammalian enzyme. Cross-resistance to rifampin has only been shown with other rifamycins. This is the probable mechanism of action by which rifampin exerts its therapeutic effects.

Absorption is more rapid when rifampin is administered one hour before meals. Peak blood levels in normal adults vary widely from individual to individual. Peak levels occur between 2 and 4 hours following the oral administration of a 600 mg dose with average peak values of 7-10 μg/mL.

Rifampin is distributed throughout the body and is detectable in many organs and body fluids, including the cerebrospinal fluid. The highest concentrations are present in the liver and bile.

In normal subjects, the biological half-life of rifampin in serum averages about 3 hours after a 600 mg oral dose, with increases up to 5.1 hours reported after 900 mg dose. Rifampin is eliminated from the blood equally in the urine and feces as unchanged drug and metabolites.

The principal metabolite in man is the biologically active desacetylrifampin. Desacetylation of rifampin in the body does not substantially modify its anti-mycobacterial activity. In Kirschner's medium, the MIC against M. tuberculosis varied from 0.1 to 2 μg/mL.

INDICATIONS AND CLINICAL USE

RIFADIN (rifampin) is indicated as a treatment of tuberculosis.

To achieve a complete kill of the bacillary population and to avoid selection of drug-resistant mutants, RIFADIN must be used concomitantly with at least one other active anti-tuberculous drug. The selection of the specific drug for partner is determined by the *in vitro* sensitivity of the

causative organisms, comparative safety and effectiveness, the patient's previous clinical history and the absorption/distribution pattern of the drug.

It is also indicated for the prophylaxis of bacterial meningitis or carriage of *N. meningitidis* or *H. influenza b* in persons exposed to a primary case.

CONTRAINDICATIONS

- Jaundice associated with reduced bilirubin excretion.
- History of previous sensitivity to any of the rifamycins.
- Premature and newborn infants in whom the liver is not yet capable of functioning with full efficiency.
- RIFADIN (rifampin) passes into the breast milk and therefore should not be used during lactation.
- RIFADIN use is contraindicated when given concurrently with the combination of saquinavir/ritonavir (see PRECAUTIONS).

WARNINGS

RIFADIN (rifampin) has been shown to produce liver dysfunction. There have been fatalities associated with jaundice in patients with liver disease or receiving RIFADIN concomitantly with other hepatotoxic agents. Since an increased risk may exist for individuals with liver disease, benefits must be weighed carefully against the risk of further liver damage. Patients with impaired liver function should only be given rifampin in case of necessity and then with caution and under strict medical supervision. In these patients, careful monitoring of liver function, especially serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) should be carried out prior to therapy and then every two to four weeks during therapy. If signs of hepatocellular damage occur, RIFADIN should be withdrawn.

In some cases, hyperbilirubinemia resulting from competition between rifampin and bilirubin for excretory pathways of the liver at the cell level can occur in the early days of treatment. An isolated report showing a moderate rise in bilirubin and/or transaminase level is not in itself an indication for interrupting treatment; rather, the decision should be made after repeating the tests, noting trends in the levels, and considering them in conjunction with the patient's clinical condition.

Rifampin has enzyme-inducing properties, including induction of delta aminolevulinic acid synthetase. Isolated reports have associated porphyria exacerbation with rifampin administration.

Clostridium difficile-associated disease

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including rifampin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see ADVERSE REACTIONS).

PRECAUTIONS

General

A complete blood count (CBC), serum creatinine and liver function tests should be obtained prior to instituting therapy and periodically throughout the course of therapy. Because of a possible transient rise in transaminase and bilirubin values, blood for baseline clinical chemistries should be obtained before RIFADIN dosing.

RIFADIN (rifampin) increases the requirements for anticoagulant drugs of the coumarin type. This effect is not observed until the fifth day following initiation of treatment. The decrease in prothrombin time usually lasts between 5 and 7 days, and is the result of RIFADIN's ability to cause induction of drug metabolizing enzyme systems of the liver. As a result, the rate of metabolism of those drugs which are substrates for these enzymes can be altered, resulting in reduced pharmacological effects of the drugs involved. In patients receiving anticoagulants, it is recommended that daily prothrombin times be performed until the dose of the anticoagulant required has been established. This is particularly important when rifampin administration is either initiated or withdrawn.

The intermittent administration of high doses of RIFADIN >120 mg/dose has been reported to be associated with a hypersensitivity reaction, characterized by fever and myalgia. The incidence of this reaction is greater when RIFADIN is given on a once-a-week basis than on a twice or thrice weekly basis. It is recommended that when resuming treatment with RIFADIN after short or prolonged interruptions, it be given in small, gradually increasing doses. During the transitional period, the renal and hemapoietic systems should be closely monitored. The drug should be stopped immediately if renal failure, thrombocytopenia purpura or hemolytic anaemia develop and should not be re-instituted.

Safe conditions for the use of ethambutol alone or in combination with RIFADIN have not been established for children under the age of thirteen years. Although renal insufficiency does not alter blood levels of RIFADIN, marked increases in ethambutol levels are observed under similar conditions; this, therefore, should be taken into consideration in such patients receiving RIFADIN /ethambutol combination therapy. Caution is recommended when instituting therapeutic regimens in which isoniazid is to be used concurrently with RIFADIN, in patients with impaired liver function, the elderly and malnourished.

From experimental studies, it would appear that bromosulphalein (BSP) and RIFADIN compete with one another at the liver cell-bile canaliculus boundary. Clinically, this phenomenon can be reflected by spurious BSP levels. It is recommended that the BSP test be carried out at least five hours after the last dose of RIFADIN.

Urine, feces, saliva, sputum, sweat and tears may be coloured red-orange by RIFADIN and its metabolites. Individuals to be treated should be made aware of these possibilities in order to prevent undue anxiety.

Patients should be advised that soft contact lenses may be permanently stained.

It has been reported that oral contraceptives have failed to prevent conception in some patients receiving RIFADIN in association with other anti-tuberculosis drugs. It is therefore necessary that alternative or additional contraceptive measures be recommended.

Use in pregnancy

Teratogenic Effects

Although rifampin has been reported to cross the placental barrier and appear in the cord blood, the effect of combinations of RIFADIN with other anti-tuberculous drugs on the human fetus is not known. No obvious effect on the fetus was detected after the administration of RIFADIN to 15 pregnant patients. An increase in congenital malformations, primarily spinabifida and cleft palate, has been reported in the offspring of mice and rats given oral doses of RIFADIN 100 mg/kg/day during pregnancy.

RIFADIN should not be used in pregnant women or women with childbearing potential. If RIFADIN therapy is judged to be essential, such treatment should be implemented only after carefully weighing the potential benefits of therapy against the risks which may be involved. In women with childbearing potential, treatment with RIFADIN should be undertaken only when the possibility of pregnancy during therapy is judged to be remote.

Non-teratogenic effects

It is not know whether RIFADIN can affect reproduction capacity.

When administered during the last few weeks of pregnancy, rifampin can cause postnatal hemorrhages in the mother and infant. In this case, treatment with vitamin K may be indicated for postnatal hemorrhage.

Nursing mothers

Rifampin is excreted in breast milk. Therefore, RIFADIN should be used in a nursing mother only if the potential benefit to the patient outweights the potential risk to the infant.

Carcinogenesis, mutagenesis, impairment of fertility

There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility. A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the drug has not been established. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampin was administered in doses two to ten times the average daily human dose for 60 weeks followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats under similar experimental conditions.

Rifampin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro*, and humans. Antitumor activity in vitro has been shown with rifampin.

There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster,* or mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin.

Drug interaction

Rifampin is a potent inducer of certain cytochrome P-450 enzymes. Coadministration of rifampin with other drugs that are metabolized through these cytochrome P-450 enzymes may accelerate the metabolism and reduce the activity of these other drugs. Therefore, caution should be used when prescribing rifampin with drugs metabolized by cytochrome P-450. To maintain optimum therapeutic blood levels, dosages of drugs metabolized by these enzymes may require adjustment when starting or stopping concomitantly administered rifampin.

Examples of drugs metabolized by cytochrome P-450 enzyme are*:* anticonvulsants (eg, phenytoin), antiarrhythmics (eg, disopyramide, mexiletine, quinidine, tocainide, propafenone), antiestrogens (eg tamoxifen, toremifen), antipsychotics (eg haloperidol), oral anticoagulants (eg warfarin) antifungals (eg, fluconazole, itraconazole, ketoconazole), antiretroviral drugs (e.g. zidovudine, saquinavir, indinavir, efavirenz), barbiturates, beta-blockers, benzodiazepines (eg diazepam), benzodiazepine-related drugs (eg zolpiclone, zolpidem), calcium channel blockers (eg, diltiazem, nifedipine, verapamil), chloramphenicol, clarithromycin, corticosteroids, cardiac glycosides preparations, clofibrate, oral contraceptives, dapsone, doxycycline, estrogens, gestrinone, oral hypoglycemic agents (sulfonylureas), immunosuppressive agents (e.g. cyclosporine, tacrolimus), irinotecan, levothyroxine, losartan, narcotic analgesics, methadone, praziquantel, progestins, quinine, riluzole, selective 5-HT3 receptor antagonists (eg ondansetron), statins metabolized by CYP 3A4, telithromycin, theophylline, thiazolidinediones (e.g.rosiglitazone), tricyclic antidepressants (eg amitriptyline, nortriptyline).

Upon completion of the treatment with RIFADIN, a renewed readjustment of the dosage should be made.

Other interaction

Atovaquone: when the two drugs are taken concomitantly, decreased concentrations of atovaquone and increased concentrations of rifampicin were observed.

Concurrent use of ketoconazole and rifampin has resulted in decreased serum concentration of both drugs. Concurrent use of rifampin and enalapril has resulted in decreased concentrations of enalaprilat, the active metabolite of enalapril. Dosage adjustments should be made if indicated by the patient's clinical condition.
Concomitant antacid administration may reduce the absorption of rifampin. Daily doses of rifampin should be given at least 1 hour before the ingestion of antacids.

Probenecid and cotrimoxazole have been reported to increase the blood level of rifampin.

When RIFADIN is given concomitantly with the combination saquinavir/ritonavir, the potential for hepatotoxicity is increased. Therefore, concomitant use of RIFADIN with saquinavir/ritonavir is contraindicated (see CONTRAINDICATIONS).

When rifampin is given concomitantly with either halothane or isoniazid the potential for hepatotoxicity is increased. The concomitant use of RIFADIN, which contains rifampin, and halothane should be avoided. Patients receiving both rifampin and isoniazid should be monitored closely for hepatotoxicity (see WARNINGS).

Plasma concentration of sulfapyridine may be reduced following the concomitant administration of sulfasalazine and rifampin. This finding may be the result of alteration in the colonic bacteria responsible for the reduction of sulfasalazine to sulfapyridine and mesalamine.

Drug/laboratory tests interaction

Therapeutic levels of rifampin have been shown to inhibit standard microbiological assays for serum folate and vitamin B_{12}. Therefore, alternate assay methods should be considered.

Transient abnormalities in liver function tests (eg, elevation in serum bilirubin, abnormal bromsulphalein [BSP] excretion, alkaline phosphatase and serum transaminases), and reduced biliary excretion of contrast media used for visualization of the gallbladder have also been observed. Therefore, these tests should be performed before the morning dose of RIFADIN.

Rifampin has enzyme induction properties that can enhance the metabolism of endogenous substrates including adrenal hormones, thyroid hormones, and vitamin D.

Cross-reactivity and false-positive urine screening tests for opiates have been reported in patients receiving rifampicin when using the KIMS (Kinetic Interaction of Microparticles in Solution) method (eg, Abuscreen OnLine opiates assay; Roche Diagnostic Systems). Confirmatory tests, such as gas chromatography/ mass spectrometry, will distinguish rifampicin from opiates.

ADVERSE REACTIONS

RIFADIN (rifampin) is usually well tolerated at recommended dosage levels.

Gastrointestinal disorders: heartburn, epigastric distress, anorexia, nausea, vomiting, gas, cramps, abdominal discomfort and diarrhea have been noted in some patients.

Occasionally, sore mouth, sore tongue associated with hypersensitivity reactions have been encountered.

Infection and infestations: Although *Clostridium difficile* has been shown *in vitro* to be sensitive to rifampin, pseudomembranous colitis has been reported with the use of rifampin (and other broad spectrum antibiotics). Therefore, it is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use (see WARNINGS).

Blood and lymphatic system disorders: Thrombocytopenia, purpura, leukopenia, hemolytic anaemia (may be related to hypersensitivity reactions) and decreased hemoglobin have been observed. Thrombocytopenia with or without purpura has occurred when RIFADIN and ethambutol were administered concomitantly according to an intermittent dose schedule twice weekly and in high doses.
Thrombocytopenia has occurred primarily with high dose intermittent therapy, but has also been noted after resumption of interrupted treatment. It rarely occurs during well-supervised daily therapy. This effect is reversible if the drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have been reported when rifampin administration has been continued or resumed after the appearance of purpura.

Disseminated intravascular coagulation has also been rarely reported.

Agranulocytosis has been reported very rarely.

Occasionally, eosinophilia associated to hypersensitivity reactions have been encountered.

Nervous system disorders: headache, drowsiness, fatigue, ataxia, dizziness, inability to concentrate, mental confusion, psychoses, behavioral changes, muscular weakness, fever, pains in extremities and generalized numbness have also been noted.

Musculoskeletal and connective tissue disorders: Rare reports of myopathy have also been observed. Bone pain (may be related to hypersensitivity reactions).

Eye disorders: Visual disturbances have been observed.

Occasionally, conjunctivitis associated with hypersensitivity reactions has been encountered.

Endocrine disorders: The following menstrual disturbances: breakthrough bleeding, spotting, amenorrhea, monthly prolongation of both menstrual interval and menses have been reported. Rare reports of adrenal insufficiency in patients with compromised adrenal function have been observed.

Renal and urinary disorders: Elevations in BUN and serum uric acid have been reported. Rarely, hemoglobinuria, hematuria, interstitial nephritis, renal insufficiency, acute tubular necrosis and acute renal failure have been noted.

These are generally considered to be hypersensitivity reactions. They usually occur during intermittent therapy or when treatment is resumed following intentional or accidental interruption of a daily dosage regimen, and are reversible when rifampin is discontinued and appropriate therapy instituted.

Skin and subcutaneous tissue disorders: cutaneous reactions are mild and self-limiting and do not appear to be hypersensitivity reactions. Typically, they consist of flushing and itching with or without a rash. More serious cutaneous reactions, which may be due to hypersensitivity, occur but are uncommon. Erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis and vasculitis have been reported on rare occasions. Occasionally, pruritis, urticaria, skin rashes and pemphigoid reaction are associated with hypersensitivity reactions.

Hepatobiliary disorders: Rarely, hepatitis or a shock-like syndrome with hepatic involvement and abnormal liver function tests has been reported. Transient abnormalities in liver function tests (elevations of serum bilirubin, BSP, alkaline phosphatase and serum transaminases) have been observed, particularly during the first few weeks of treatment (see WARNINGS section).

A few cases of jaundice with evidence of hepatocellular damage have been reported in patients receiving RIFADIN. In some of them it was possible, under careful laboratory control, to resume treatment after an interval without recurrence of abnormalities.

Immune system disorders: Immunological reactions (including anaphylaxis) with shortness of breath, wheezing, decrease in blood pressure and shock have occurred with intermittent dosage regimens. Other reactions which have occurred with intermittent dosage regimens include "flu" syndrome (such as episodes of fever, chills, headache, dizziness, bone pain and malaise).

The "flu" syndrome may also appear if rifampin is taken irregularly by the patient or if daily administration is resumed after a drug free interval. It rarely occurs during well-supervised daily therapy.

Occasionally, hypersensitivity reactions such as: pruritis, urticaria, skin rashes, pemphigoid reaction, eosinophilia, sore mouth, sore tongue, conjunctivitis, acute hemolytic anemia and acute renal failure (usually due to acute tubular necrosis or to acute interstitial nephritis) have been observed.

Investigations: decrease in blood pressure (associated with hypersensitivity reactions).

Respiratory, thoracic and mediastinal disorders: shortness of breath and wheezing are generally associated to hypersensitivity reactions.

Miscellaneous: Edema of the face and extremities has been reported.

Clinical trials have furnished no evidence to suggest that RIFADIN has any harmful effects on the cochleovestibular system.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

The minimum acute lethal or toxic dose is not well established. However, non fatal acute overdoses in adults have been reported with doses ranging from 9 to 12 g rifampicin. Fatal acute overdoses in adults have been reported with doses ranging from 14-60 g. Alcohol or a history of alcohol abuse was involved in some of the fatal and non-fatal reports.

Nonfatal overdoses in pediatric patients ages 1 to 4 years old of 100 mg/kg for one to two doses has been reported.

Signs and Symptoms

Nausea, vomiting, abdominal pain, pruritus, headache and increasing lethargy will probably occur within a short time after acute ingestion; unconsciousness may occur when there is severe hepatic disease. Brownish-red or orange discoloration of the skin, urine, sweat, saliva, tears, and feces will occur, and its intensity is proportional to the amount ingested. Facial or periorbital edema has also been reported in pediatric patients. Hypotension, sinus tachycardia, ventricular arrhythmias, seizures and cardiac arrest were reported in some fatal cases.

Liver enlargement, possibly with tenderness, can develop within few hours after severe overdosage; bilirubin levels may increase and jaundice may develop rapidly. Hepatic involvement may be more marked in patients with prior impairment of hepatic function. Other physical findings remain essentially normal. A direct effect upon the hematopoietic system, electrolyte levels, or acid-base balance is unlikely.

Management

In the event of an acute oral overdose activated charcoal may be considered. General supportive measures are recommended and individual symptoms should be treated as they arise.

Antiemetic medication may be required to control severe nausea and vomiting. Active diuresis (with measured intake and output) will help promote excretion of the drug. Hemodyalisis may be of value in some patients. No specific antidote is known.

DOSAGE AND ADMINISTRATION

Treatment of tuberculosis

Adults

600 mg in a single daily dose. Should intolerance occur, the daily dosage may be reduced to 450 mg. In patients with impaired liver function, a daily dose of 8 mg/kg should not be exceeded. A daily dosage of 10 mg/kg is recommended for frail and elderly persons.

Children

10 to 20 mg/kg not to exceed 600 mg/day. Data is not available for the determination of dosage for children under 5 years of age.

In treatment of pulmonary tuberculosis, RIFADIN (rifampin) must be used in conjunction with at least one other anti-tuberculous agent. In general, therapy should be continued until bacterial conversion has been established and maximum clinical improvement has occurred.

To ensure optimum absorption, RIFADIN should be taken on an empty stomach (1 hour before breakfast).

Prophylaxis versus *H. influenza type b*

Adults:	600 mg every 24 hours x 4 days
Children (≥1 month):	20 mg/kg (up to 600 mg) every 24 hours x 4 days
Neontates (<1 month):	10 mg/kg every 24 hours x 4 days

Prophylaxis versus *N. meningitidis*

Adults:	600 mg every 12 hours x 2 days
Children (≥1 month):	10 mg/kg (up to 600 mg) every 12 hours x 2 days
Neontates (<1 month):	5 mg/kg every 12 hours x 2 days

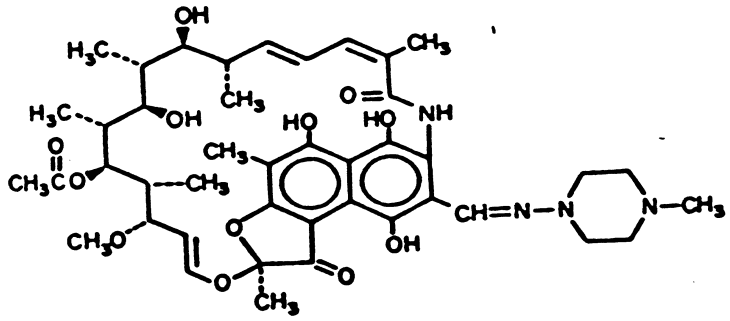
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: RIFAMPIN

Chemical Name: 5,6,9,17,19,21-hexahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-[N-(4-methyl-1-piperazinyl)formimidoyl]-2,7-(epoxypentadeca [1,11,13] trienimino) naphtho [2,1-*b*]furan-1,11(2H)-dione 21-acetate

Structural formula: $C_{43}H_{58}N_4O_{12}$



Molecular weight: 822.94

Description: RIFADIN is an orange to red-brown, tasteless, crystalline powder. It is highly soluble in chloroform and methylene chloride, readily soluble in methyl alcohol and ethyl acetate, and poorly soluble in acetone and water. Its melting point is 183-188°C.

AVAILABILITY OF DOSAGE FORMS

Each capsule contains: RIFADIN (rifampin) 150 mg (opaque maroon and opaque scarlet) or 300 mg (opaque maroon and opaque scarlet).

Non-medicinal ingredients: corn starch, D&C Red #28, FD&C Blue #1, FD&C Red #40, gelatin, magnesium stearate, titanium dioxide and white ink. Tartrazine-free.

Available in bottles of 100 capsules.

MICROBIOLOGY

Anti-mycobacterial activity

The minimum inhibitory concentration of RIFADIN (rifampin) for Mycobacterium tuberculosis in vitro, varies considerably with the technique used.
Rifampin inhibited 20 strains of Mycobacterium tuberculosis in concentrations of 0.005 to 0.02 μg/mL in 7H-9 broth with Tween 80 and killed all or nearly all of the inoculum in four to eight times greater concentrations. In the same medium without Tween 80, as well as on 7H-10 agar, about 16 to 64 times these amounts were required to produce the same effect (Lorian & Finland, 1969). The susceptibility of a range of typical and atypical Mycobacterial to rifampin in Dubos medium is given in the following table:

IN VITRO

ACTIVITY OF RIFAMPIN ON COLLECTION STRAINS OF MYCOBACTERIAL IN DUBOS MEDIUM

STRAIN	MIC μg/mL	STRAIN	MIC μg/mL
M. tuberculosis $H_{37}Rv$	0.2	M. smegmatis ATCC 607	100
M. tuberculosis $H_{37}Ra$	0.2	M. smegmatis 63	200
M. tuberculosis Abate	0.2	M. chelonei NCTC 946	100
M. tuberculosis Schiava	0.1	M. phlei 54	0.1
M. bovis Vallée	0.1	M. phlei Timoteo	0.1
M. bovis BCG	0.05	M. thamnopheos	0.1
M. avium Poulet T_3	10	M. marinum	0.1
M. avium Bang	0.1	M. ranae (fortuitum)	100
M. avium $Faisan_2$	5	M. kansasii	0.5
M. avium $Faisan_4$	2	M. scrophulaceum	0.2
M. avium Kirchenberg	20	M. intracelluare	0.1

Resistance Pattern

The incidence of primary resistance to rifampin in tuberculosis was found not to exceed 0.4 percent (Hobby et al., 1970).

The mutation rates of M. tuberculosis and M. kansasii toward resistance levels of roughly 10, 50 and 200 times the MIC of rifampin were found to range from 10^{-5} to 10^{-7}. These relatively high values show that drug resistance to rifampin is of the streptomycin type. Consequently, monotherapy of human tuberculosis associated with a bacterial count greater than 10^{-7} involves a high risk of selecting rifampin-resistant organisms through the killing of the rifampin-sensitive population. (Manten et al., 1969). Mycobacterial resistant to 80 μg/mL have been observed in patients under treatment for tuberculosis. Resistant strains may sometimes be isolated from patients treated with different drug combinations.

No cross-resistance with any of the known anti-tuberculous drugs or with antibiotics other than those in the rifamycin series has been demonstrated.

PHARMACOLOGY

Absorption

Rifampin is readily absorbed from the gastrointestinal tract. Peak blood levels in normal adults vary widely from individual to individual. Peak levels occur between 2 and 4 hours following the oral administration of a 600 mg dose with average peak values of 7-10 μg/mL. Absorption of rifampin is reduced when the drug is ingested with food.

Cumulation was noted upon multiple dosages of RIFADIN (rifampin) 10 mg/kg/day to newborns. Peak values appeared to be delayed in the newborns which were not seen in children up to 18 months of age. It is suggested that the drug is less readily eliminated from the newborn, probably because of the low flow of bile during the first days of life. In all of these children and infants, the main serum level of rifampin corresponded to one-third to one-tenth the levels in adults receiving proportionally the same dose (Acocella et al., 1969).

Absorption is more rapid when rifampin is administered one hour before meals. The following data were reported by Furesz et al., 1967.

SERUM LEVELS OF RIFAMPIN (μg/mL) AFTER ORAL ADMINISTRATION OF A SINGLE 150 mg DOSE

	2		4		6	
Pt. No.	Fasting	After Meal	Fasting	After Meal	Fasting	After Meal
1	0.37	0	0.32	0	0	0.90
2	2.70	0	1.37	1.60	0.49	1.30
3	1.55	0	0.75	0.14	0.20	0.31
4	1.82	0	1.02	0	0.34	0.16
5	1.77	1.65	0.86	1.00	0.19	0.21

Distribution

Rifampin is distributed throughout the body and is detectable in many organs and body fluids, including the cerebrospinal fluid. The highest concentrations are present in the liver and bile. Rifampin is about 80% protein bound. Most of the unbound fraction is not ionized and therefore is diffused freely in tissues.

Biological Half-Life

In normal subject, the biological half-life of rifampin in serum averages about 3 hours after a 600 mg oral dose, with increases up to 5.1 hours reported after 900 mg dose. Biliary obstruction causes a longer half-life, but kidney blockage does not appear to cause a change. With repeated administration, the half-life decreases and reaches average values of approximately 2 to 3 hours. The half-life does not differ in patients with renal failure at doses not exceeding 600 mg daily and, consequently, no dosage adjustment is required. The half-life of rifampin at a dose of 720 mg daily has not been established in patients with renal failure. Refer to the WARNINGS section for information regarding patients with hepatic insufficiency.

THE FOLLOWING TABLE SUMMARIZES THE HALF-LIFE VALUES REPORTED IN VARIOUS CONDITIONS

SUBJECTS	DOSAGE	BIOLOGICAL HALF-LIFE
Normal Adults*	300 mg	1-3 hours
Obstruction of** common bile duct (1 patient)	300 mg 300 mg	14 hours before operation 4-5 hours after operation
Anuria** Patient #1 Patient #2 Patient #3	 300 mg 300 mg 300 mg	 3.1 hours 2.8 hours 1.8 hours
37 children*** 12 children***	10 mg/kg 20 mg/kg	 1.2-5.6 hours

*L. Dettili, 1968; ** P. Spring, 1986; *** B. Krauer, 1968.

Excretion

Rifampin is eliminated from the blood equally in the urine and feces as unchanged drug and metabolites. Approximately half of the original dose eliminated by the bile is unchanged drug.

The proportion of unchanged drug to metabolite is less in the urine than in the bile.

In the presence of complete renal shutdown, the drug is excreted entirely in the bile.

The principal metabolite in man is the biologically active desacetylrifampin. Its excretion appears to be a dynamically changing picture at all times. This can be seen in the following table, giving the details of fluid levels of desacetylrifampin after an intravenous dose of 300 mg ^{14}C-rifampin to a patient with a biliary fistula (Keberle et al., 1968).

Souce	Time After Medication	Rifampin	Percent of total radioactivity in the collection samples as: Desacetylrifampin
Plasma	0.5 hour	93%	5%
	1 "	77%	12%
	3 hours	62%	18%
Bile	1-1.5 hours	39%	49%
	3-3.5 hours	14%	58%
	4-4.5 hours	8%	79%
	0-24 hours	43% of radioactivity administered is in bile	
Urine	0-4 hours	69%	17%
	0-24 hours	21% of radioactivity administered is in urine	

Desacetylation of rifampin in the body does not substantially modify its anti-mycobacterial activity. In Kirschner's medium, the MIC against M. Tuberculosis varied from 0.1 to 2 μg/mL.

Transplacental Transfer of Rifampin

Rifampin was administered orally to 20 women at the end of pregnancy in a dose of 300 mg (3.75-5.00 mg/kg) at intervals of 8-12 hours for various lapses of time. Maternal and fetal bloods were collected at parturition. In 5 cases, amniotic fluid was taken. Rifampin (detected by microbiological assay) rapidly crossed both blood-placental barrier and the chorion, being present in large amounts in fetal blood and amniotic fluid. The maternal blood level of rifampin was higher than the known values for male subjects. It was concluded that the fetus eliminates the drug more slowly than does the mother. Nevertheless, the amount of rifampin found in fetal blood is always less than that of the mother and after repeated dosage, the ratio is about 1:3 (Termine et al., 1970).

TOXICOLOGY

The toxicity of RIFADIN (rifampin) has been determined in various species of laboratory animals. With the exceptions of the dog and rhesus monkey, animals, including the mouse, rat rabbit and cynomolgus monkey satisfactorily tolerated oral doses of rifampin administered over a 2 to 26 week period. These doses were at least ten-fold the therapeutic dose recommended for man.

Acute Toxicity

The LD_{50} within 5 days, in the mouse, rat and rabbit is as follows:

Species	Route	No. of Dose Levels	No. of Animals/ Dose	LD_{50} (mg/kg)	95% Confidence Limits (mg/kg)
Mouse	i.p.	4	20	621	595-647
Mouse	oral	5	22	858	829-888
Rat	i.p.	5	16	533	515-552
Rat	oral	6	10	1668	1303-2135
Rabbit	oral	1	8	1550	---

LD_{50} based on the statistical method of Litchfield-Wilcoxon i.p. - intraperitoneal (Serralunga, 1967).

Rifampin given in combination with isoniazid or PAS to mice and rats, or with streptomycin sulfate to rats, did not demonstrate any increased acute toxicity of any of the drugs.

Subacute Toxicity

The cynomolgus monkey, dog and mouse, received oral doses of rifampin for periods of 1-13 weeks and in the rat, both oral and peritoneal administration was given for the same duration. Adverse effects were not observed in mice administered rifampin orally at dose levels inclusive of 100 mg/kg, or in rats administered 100 mg/kg. Parenteral doses of 100 mg/kg similarly did not produce adverse effects in the rat.

In the dog, oral doses of 100 mg/kg were toxic. Abnormalities were seen in behaviour, physical condition, renal and hepatic function tests and hemograms of these animals. After four to six weeks of treatment, death occurred in 50% of the treated animals, characterized pathologically by leukopenia, icterus, ascites, enteritis, and hepatic and renal degeneration. Icterus and moderate renal degeneration were also observed in the remaining animals. Occasional behaviour abnormalities and mild alterations in transaminase, alkaline phosphatase and protein values, were observed following a daily dose of 25 mg/kg of rifampin, administered over a period of

four to thirteen weeks. No toxic effect was produced in dosage levels under 25 mg/kg/day.

Short-term (4-13 weeks) studies in the cynomolgus monkey demonstrated mild fatty changes and sporadic sublobar foci of necrosis in the livers of some monkeys; however, this could not be specifically related to drug administration.

A moderate loss of appetite and weight occurred in some monkeys receiving 105 mg/kg over a 90-day period; there were no other apparent toxic effects of the drug.

Rifampin given for a period of thirty days, alone and in combination with ethambutol, isoniazid, PAS or streptomycin sulfate to rats, in drug ratios proposed for human clinical trials, showed that the rat can satisfactorily tolerate oral doses of rifampin and of rifampin combinations without developing significant adverse effects.

Chronic Toxicity

Rats

Six-month chronic toxicity studies using doses of rifampin up to 200 mg/kg/day had no effect on body weight, hematology or gross and microscopic pathology of the animals.

Dogs

Six-month studies showed the same toxic effects as those seen in the short-term studies. Oral doses of 25 or 50 mg/kg/day caused emesis, anorexia, diarrhea, slight depression and ataxia; three animals died during the first seven weeks of treatment. Serum transaminase, alkaline phosphatase and bromsulfophthalein retention values were increased, while the albumin, total protein, erythrocyte and hemoglobin levels were decreased. Gross and histomorphologic examinations revealed that animals given 25 and 50 mg/kg/day had a hemorrhagic enteritis, degenerative hepatic and renal alterations, but these changes were not evident in the group given 12.5 mg/kg/day.

Cynomolgus Monkeys

In a six month study, oral doses of 15, 45, 75 and 105 mg/kg/day were administered. Some monkeys exhibited emesis and lethargy in the early phase of treatment. Hematologic, clinical chemistry and urinalysis examination results of treated animals were the same as those of the control animals, with the exception of one monkey on 105 mg/kg/day, which had an elevated alkaline phosphatase. The sacrificed animals failed to reveal any evidence of systemic toxic effects from administration of the drug following gross and microscopic examinations.

Rhesus Monkeys

During the first 30 days of an 18-month study of rifampin, administered orally in doses of 40, 80 and 120 mg/kg, nephrotoxicity developed. Kidney examinations showed many of the characteristics of acute and/or subacute glomerulonephritis, suggestive of target-organ effect. This target-organ-like effect on the kidney seems to be related specifically to the rhesus monkey, as cynomolgus monkeys, studied for a longer period of time, did not exhibit a similar toxicity.

In another study, doses of 40, 80 and 120 mg/kg administered orally to cynomolgus monkeys, failed to induce a renal target-organ effect, or other significant drug-related adverse reactions.

Carcinogenicity

There are no known human data on long-term potential for carcinogenicity, mutagenicity, or impairment of fertility. A few cases of accelerated growth of lung carcinoma have been reported in man, but a causal relationship with the drug has not been established. An increase in the incidence of hepatomas in female mice (of a strain known to be particularly susceptible to the spontaneous development of hepatomas) was observed when rifampicin was administered in doses two to ten times the average daily human dose for 60 weeks followed by an observation period of 46 weeks. No evidence of carcinogenicity was found in male mice of the same strain, mice of a different strain, or rats under similar experimental conditions.

Rifampin has been reported to possess immunosuppressive potential in rabbits, mice, rats, guinea pigs, human lymphocytes *in vitro*, and humans. Antitumor activity *in vitro* has been shown with rifampin.

Mutagenicity

Increased frequency of chromosomal aberrations was observed *in vitro* in lymphocytes obtained from patients treated with combinations of rifampin, isoniazid, and pyrazinamide and combinations of streptomycin, rifampin, isoniazid, and pyrazinamide.

There was no evidence of mutagenicity in bacteria, *Drosophila melanogaster*, or mice. An increase in chromatid breaks was noted when whole blood cell cultures were treated with rifampin.

Fetal Toxicity and Teratogenicity

Mice

No maternal toxic effects were demonstrated when pregnant mice were given oral doses of 50 to 200 mg/kg of rifampin. A decrease in the average weight was noted in the fetuses of test animals receiving oral doses of 150 mg/kg and exencephaly was seen in 4% of the fetuses. An increase in

the incidence of resorptions and a decrease in fetal numbers also occurred at an oral dose of 200 mg/kg. Skeletal abnormalities characterized by an absence of ossification also occurred on doses of 200 mg/kg. On oral doses of 50-100 mg/kg and 150-200 mg/kg, dose-dependent cleft palate abnormalities occurred with a range of 0.6%-0.72% and 3.69%-18.2%, respectively.

Rats

A maternal toxic effect occurred with oral doses of 200 mg/kg and over. Reductions in the number of fetuses and fetal weights, with an increase of resorptions, were seen following oral doses of 100 and 200 mg/kg. Spina bifida was observed with oral doses of 150 mg/kg and the incidence of this teratogenic abnormality increased with higher doses. On a dosage of 200 mg/kg, rhachischisis in the lumbosacral region and incomplete ossification centre development, particularly of the sternebrae, were noted.

In one study, following administration of rifampin in doses of 200 mg/kg, microcephaly was detected in 0.4% of the fetuses and microphthalmia in 1.2%. No adverse effect on lactation or on the suckling young was noted when oral doses of 50 and 100 mg/kg had been administered to female rats during the last trimester of pregnancy.

Rabbits

Doses of rifampin, 200 and 300 mg/kg/day produced a high mortality rate of the dams and toxic effects including anorexia, weight loss and abortion were produced in pregnant rabbits on oral doses of 75 and 150 mg/kg. Embryotoxic effects resulting in increased resorptions were evidenced following oral doses of 150 mg/kg. This species did not demonstrate any major malformations which could be attributed to the drug.

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