

Rifampin

Brand Name: Rifadin, Rifadin IV, Rimactane



Drug Description

Rifampin is a semisynthetic, broad-spectrum antibiotic derivative of rifamycin B, which was derived from *Streptomyces mediterranei*. [1]

HIV/AIDS-Related Uses

Rifampin is used alone or in combination as an alternative to rifabutin or other rifamycins in the treatment of latent tuberculosis (TB) infection. The combination regimen of rifampin/pyrazinamide also has been used to treat latent TB infection in HIV infected patients. However, studies indicate that this drug combination can cause severe, sometimes fatal, liver damage. Risk factors associated with toxicity include a history of liver disease, alcohol use, or isoniazid-induced liver damage. Rifampin/pyrazinamide is contraindicated in patients with these risk factors. The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society recommend considering the regimen for latent TB infection only in carefully selected individuals, under the care of a clinician with expertise in the treatment of latent TB infection, if the potential benefits of the regimen outweigh the risk for severe liver injury and death, and when the preferred or alternative regimens are judged unlikely to be completed. The combination regimen may be used to treat active TB because the risks from the active disease are much greater than those posed by the latent disease.[2]

The use of rifampin to treat active TB was previously contraindicated in patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). However, the CDC has indicated that rifampin can be used when the antiretroviral regimen includes either efavirenz and two nucleoside reverse transcriptase inhibitors (NRTIs); ritonavir and one or more NRTIs; or the combination of two PIs (ritonavir and either saquinavir hard-gel capsule or saquinavir soft-gel capsule).[3]

Rifampin is also used in conjunction with other medications to treat *Mycobacterium avium* complex (MAC) in HIV infected individuals.[4]

Non-HIV/AIDS-Related Uses

Rifampin is used in conjunction with other antituberculosis agents for treatment of active TB. It is used alone and in combination with other drugs for treatment of latent TB infection and for treatment of atypical mycobacterial infections, including MAC and leprosy.[5]

Rifampin is used for prevention of *Neisseria meningitidis* infections, including chemoprophylaxis for individuals in close contact with people with invasive meningococcal disease or for outbreak control in small populations. It is also used to prevent *Haemophilus influenzae* type b infection of individuals in close contact with patients infected by this organism. Rifampin is used in combination with other medications to treat serious infections caused by *Streptococcus* and *Staphylococcus* species, including methicillin- and multidrug-resistant strains.[6]

Rifampin is used as part of a multidrug parenteral regimen for treatment of inhalational anthrax. It is also used as an adjunct to other anti-infective agents for treatment of brucellosis, *Legionella*, and *Rhodococcus* infections.[7]

Pharmacology

Rifampin suppresses the initiation of RNA chain formation in susceptible bacteria by inhibiting DNA-dependent RNA polymerase. The site of action appears to be the beta subunit of the enzyme. Rifampin is most active during bacteria cell division, although it retains some effect when bacteria are in the metabolic resting state.[8]

Rifampin is well absorbed from the gastrointestinal tract. Following a 600 mg oral dose of rifampin in fasting adults, peak plasma concentrations (C_{max}) average 7 mcg/ml and are reached within 2 to 4 hours. Following a 300 or 600 mg dose of rifampin given via IV infusion over 30 minutes, C_{max} averages 9 or 17.5 mcg/ml, respectively, and plasma concentrations remain detectable for 8 or 12 hours, respectively. In children given a 10 mg/kg oral dose of rifampin, peak serum concentrations range from 3.5 to 15 mcg/ml. Rifampin C_{max} may range from 4 to 32 mcg/ml, depending on

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Pharmacology (cont.)

interpatient variation. Individuals with hepatic impairment experience higher and more prolonged rifampin plasma concentrations.[9]

Rifampin is distributed into most body tissues and fluids, including ascitic fluid, bile, bone, cerebrospinal fluid (CSF), the liver, the lungs, pleural fluid, the prostate, saliva, seminal fluid, and tears. CSF concentrations of rifampin in patients with inflamed meninges are reported to be 10% to 20% of concurrent plasma concentrations.[10]

Rifampin is in FDA Pregnancy Category C. It crosses the placenta and in rare cases has caused postnatal hemorrhage in the mother and infant when given in the last few weeks of pregnancy. Congenital malformations have been reported in rodents at doses greatly exceeding the usual daily human dose. Rifampin is distributed into breast milk; however, no problems have been documented in humans.[11]

Protein binding is high (89%). Rifampin is rapidly metabolized by hepatic microsomal oxidases to an active metabolite, 25-O-desacetyl-rifampin, and also to inactive metabolites. Elimination half-life is 3 to 5 hours initially and decreases to 2 to 3 hours with repeated administration. The half-life in patients with renal impairment may increase from 5 to 11 hours. Rifampin is enterohepatically recirculated, but the active deacetylated metabolite is not. Approximately 6% to 15% of the unchanged drug and 15% of the active deacetylated metabolite is excreted in urine. Approximately 60% to 65% of a dose is excreted in feces via biliary elimination. Plasma concentrations are not appreciably affected by hemodialysis or peritoneal dialysis.[12] [13]

Adverse Events/Toxicity

The most common adverse effects of rifampin include abdominal cramping, diarrhea, heartburn, nausea, and vomiting.[14] Rifampin has been associated with a flu-like syndrome of chills, difficult breathing, dizziness, fever, headache, muscle and bone pain, and shivering. Intermittent use of rifampin may increase the chance of developing the flu-like syndrome, acute hemolysis, or renal failure.[15] A reversible, lupus-like

syndrome characterized by arthritis, malaise, myalgias, and peripheral edema has been reported in some patients receiving concomitant therapy of rifampin and either clarithromycin or ciprofloxacin, as a result of inhibited hepatic metabolism of rifampin.[16]

Rarely, blood dyscrasias, hepatitis, hepatitis prodromal symptoms, and interstitial nephritis have been reported with rifampin use.[17] Jaundice-associated fatalities and hepatitis have occurred in patients with pre-existing liver disease or who were receiving other hepatotoxic medications.[18]

Hypersensitivity (itching, redness, and rash) and fungal overgrowth of the mouth or tongue have also been reported. In addition, rifampin may discolor body fluids, giving a red-orange or red-brown color to urine, feces, saliva, skin, sweat, and tears. Discolored tears may permanently stain soft contact lenses.[19]

Drug and Food Interactions

If rifampin is administered with food, C_{max} may be slightly reduced (approximately 30%) and delayed.[20] To ensure maximum absorption, rifampin should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal.[21]

Rifampin and other rifamycin derivatives markedly induce cytochrome P-450 (CYP) oxidases, accelerating the metabolism of HIV PIs (amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, and saquinavir) and NNRTIs (delavirdine, nevirapine, efavirenz), resulting in subtherapeutic plasma concentrations of the antiretroviral agents (see HIV/AIDS-Related Uses section). Nevirapine and efavirenz, despite diminished plasma concentrations, may be used successfully with rifampin when absolutely necessary.[22]

Rifampin can also affect the metabolism of certain NRTIs, including zidovudine. In addition, PIs and some NNRTIs (e.g., delavirdine) may reduce the metabolism of rifamycins, leading to increased plasma concentrations and increased toxicity of the rifamycins. Because these drug interactions are complex, experts in the management of

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Drug and Food Interactions (cont.)

mycobacterial infections in HIV infected patients should be consulted.[23]

Administration of rifampin with other medications metabolized by hepatic enzymes alters the metabolism of these other drugs. Rifampin induces CYP metabolism, thus decreasing the plasma concentration and efficacy, of the following drugs: theophylline; azole antifungals; antiarrhythmic agents (disopyramide, mexiletine, propafenone, quinidine, and tocainide); antidiabetic agents (chlorpropamide, glyburide, and tolbutamide); chloramphenicol; coumarin anticoagulants; digoxin; corticosteroids; methadone; phenytoin; and verapamil. Rifampin also induces the metabolism and decreases the enterohepatic cycling of estrogen-containing oral contraceptives, causing a decrease in hormone levels and contraceptive efficacy.[24]

Concomitant use of aluminum or magnesium hydroxide antacids with rifampin may decrease absorption of rifampin, requiring rifampin administration one hour prior to the antacid.[25]

Concurrent use of rifampin and other hepatotoxic substances, including but not limited to isoniazid and alcohol, increases the potential for hepatotoxicity.[26] Daily regimens of rifampin/pyrazinamide used to treat latent TB infection appear to cause severe liver injury and fatality.[27]

Contraindications

Rifampin is contraindicated in patients with hepatic function impairment and in those with a history of hypersensitivity reaction to rifampin or to any of the rifamycins.[28]

Concomitant use of rifampin with unboosted saquinavir or saquinavir mesylate results in reduced plasma concentrations of saquinavir and is contraindicated.[29]

Recent data from a 28-day Phase I clinical trial of rifampin 600 mg once daily and saquinavir/ritonavir 1000 mg/100 mg twice daily showed significant hepatocellular toxicity in nearly

40% of patients. Transaminase elevations of up to 20 times the upper limit of normal were noted. Following drug discontinuation, clinical symptoms abated and liver function tests began returning to normal in all affected patients. Based on this data, the saquinavir manufacturer recommends that rifampin not be administered to patients taking ritonavir-boosted saquinavir as part of combination antiretroviral therapy.[30]

Clinical Trials

For information on clinical trials that involve Rifampin, visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: Rifampin AND HIV Infections.

Dosing Information

Mode of Delivery: Oral; intravenous.[31]

Dosage Form: Capsules containing 150 mg or 300 mg.[32]

Powder for injection containing 600 mg per vial, with preservative, and reconstituted with 10 ml sterile water for injection.[33]

Capsules in fixed-dose combination with isoniazid (rifampin 300 mg and isoniazid 150 mg).[34]

Tablets in fixed-dose combination with isoniazid and pyrazinamide (rifampin 120 mg, isoniazid 50 mg, and pyrazinamide 300 mg).[35]

Oral compounded suspension containing 10 mg/ml in simple syrup.[36]

Contents of rifampin capsules may be mixed with applesauce or jelly or used to compound a suspension for oral use.[37]

Storage: Rifampin capsules should be stored in a tight, light-resistant container at 15 C to 30 C (59 F to 86 F). Rifampin for injection should be stored below 40 C (104 F) in a tight, light-resistant container. The compounded suspension should be stored in a tight, light-resistant, amber glass or plastic prescription bottle at controlled room temperature of 22 C to 28 C (71.6 F to 82.4 F) or under refrigeration at 2 C to 8 C (35.6 F to 46.4

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Dosing Information (cont.)

F).[38] [39]

Chemistry

CAS Name: Rifamycin, 3-[[[(4-methyl-1-piperazinyl)imino]methyl]-[40]

CAS Number: 13292-46-1[41]

Molecular formula: C43-H58-N4-O12[42]

C62.76%, H7.10%, N6.81%, O23.33%[43]

Molecular weight: 822.94[44]

Physical Description: Rifampin occurs as a red-brown, crystalline powder.[45]

Stability: Compounded oral rifampin suspension should be discarded 30 days after the day of compounding.[46]

Suspension must be shaken prior to administration.[47]

After reconstitution with sterile water for injection, the parenteral solution of 60 mg/ml is stable at room temperature for 24 hours. After rifampin dilution in 100 or 500 ml normal saline, the solution may be stable at room temperature for up to 24 hours. After a similar dilution in 5% dextrose in water, the solution is stable at room temperature for up to 4 hours.[48] [49]

Solubility: Rifampin is very slightly soluble in water and slightly soluble in alcohol.[50]

Other Names

Rifampicina[51]

Rifamycin AMP[52]

Further Reading

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Manufacturer Information

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For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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