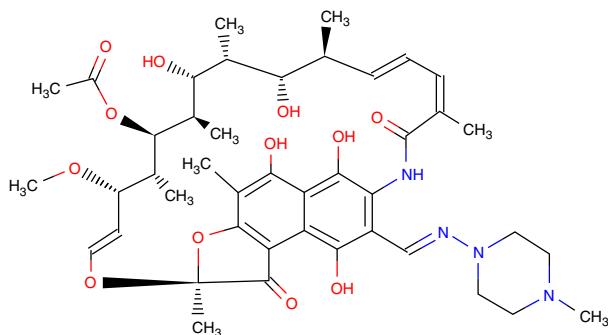


Rifampin

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- Name: Rifampin
- Chemical Abstracts Service Registry Number: 13292-46-1
- Synonyms: Rifampicin
- Molecular Formula: C₄₃H₅₈N₄O₁₂
- Chemical Structure:



Background

Rifampin was developed in the Dow-Lepetit Research Laboratories in Milan, Italy, as part of a program of chemical modification of the rifamycins, the natural metabolites of *Nocardia mediterranei*. Modifications of most of the functional groups of the rifamycin molecule were performed with the objective of finding a derivative that was active when administered orally. Rifampin was discovered to be the most active in the oral treatment of infections in animals and, after successful clinical trials, was introduced into therapeutic use in 1968. A large number of clinical and biological studies have confirmed the important role of rifampin in therapy for tuberculosis and other selected infectious diseases.

Uses

Rifampin is used as an antibiotic. It is a semisynthetic derivative of rifamycin B, a macrocyclic antibiotic produced by the mold *Streptomyces mediterranei*. Rifampin is used for the treatment of tuberculosis, brucellosis, *Staphylococcus aureus*, and other infectious diseases.

Environmental Fate and Behavior

Physicochemical Properties

Rifampin or rifampin is a red to orange odorless powder. It is very slightly soluble in water (1 g per 762 ml at pH <6), acetone, carbon tetrachloride, ethanol, and ether; freely soluble in chloroform and dimethyl sulfoxide (DMSO); soluble in ethyl acetate and methanol and tetrahydrofuran. The solubility

of rifampin increases at acidic pH. Rifampin has a melting point of 138–188 °C and a pK_a of 1.7 related to the 4-OH moiety and 7.9 related to the 3-piperazine nitrogen moiety. In 1% suspension in water, the pH is 4.5–6.5.

Exposure Pathway

Ingestion is the most common route of exposure. Rifampin is available in oral and parenteral forms.

Toxicokinetics

Rifampin is rapidly and nearly completely absorbed from the gastrointestinal tract. Peak serum levels are seen within 2–4 h. Food, antacids, ketoconazole, and aminosalicic acid interfere with absorption and delay peak levels. If these agents are used concurrently, they should be administered separately at an interval of at least 8 h. Massive ingestions in the overdose setting may also delay absorption. Protein binding is 75–90%. The volume of distribution is approximately 1 l kg⁻¹. Rifampin undergoes hepatic deacetylation to an active metabolite. Both rifampin and its deacetylated metabolite are excreted into the bile. Rifampin and to a lesser extent its deacetylated metabolite undergo enterohepatic recirculation. The half-life of therapeutic doses of rifampin is 1.5–5 h. The half-life is shortened after regular use due to induction of hepatic enzymes. Chronic liver disease increases the half-life. The kinetics are not well described in the overdose setting.

Mechanism of Toxicity

In the acute overdose setting, the mechanism of toxicity is not defined. A number of toxic reactions occurring with intermittent dosing schedules or on reexposure are postulated to be due to the presence of antirifampin antibodies.

Acute Toxicity

Human

Intentional overdoses of rifampin rarely lead to significant morbidity, and fatalities are exceedingly uncommon. The few deaths that have been associated with rifampin have all been in individuals with a history of alcoholism or concomitant ethanol ingestion. Acute overdose with rifampin may cause a red to orange discoloration of the skin, 'the red man syndrome' seen within 2 h of exposure. Body fluids are also discolored and urine, feces, sweat, tears, and saliva may exhibit a red to orange discoloration. Symptoms associated with rifampin overdose include headache, abdominal pain, nausea,

vomiting, and flushing. Pruritus, which may be limited to the scalp, may be seen, and a cutaneous burning sensation may be noted. Lethargy and obtundation have been reported. Facial or periorbital edema may be seen. Minor and transient elevations of hepatic transaminases, bilirubin, and amylase have been reported. Rifampin may inhibit bilirubin excretion and may interfere with the bilirubin assay. An acute ingestion of 60 g was fatal in an alcoholic. Overdoses of 12 g in otherwise healthy individuals have been tolerated, as has 2 g in an 18-month-old. Because of the small number of cases, correlation of dose with severity is not possible, and serum levels are not useful.

Animal

Rifampin is used to treat certain types of infections in various animals and can cause toxicity similar to that seen in humans. Adverse effects in horses are rare when rifampin is given orally, although central nervous system depression, sweating, hemolysis, and anorexia have been reported in equines receiving rifampin.

In mice the LD₅₀ for intraperitoneal administered rifampin is 640 mg kg⁻¹. The intravenous and oral LD₅₀s are 260 and 829.3 mg kg⁻¹, respectively. The LD₅₀ for rats intraperitoneally administered rifampin is 550 mg kg⁻¹. The intravenous and oral LD₅₀s are 330 and 1303.3 mg kg⁻¹, respectively.

Chronic Toxicity

Human

Rifampin used daily at therapeutic doses is associated with facial flushing and itching in less than 5% of patients. More rarely, hepatotoxicity is seen and may lead to complete hepatic failure requiring liver transplantation. The risk of hepatotoxicity is increased with chronic liver disease, alcoholism, and old age. Acute renal failure, interstitial nephritis, nephrogenic diabetes insipidus, and thrombocytopenic purpura are rare complications of continuous use. The use of rifampin on an intermittent dosing schedule, two or three times weekly or less, is associated with a higher incidence of toxic side effects. These include a flulike syndrome with that lasts up to 8 h following each dose of rifampin. More serious toxic effects associated with an intermittent dosing schedule include hemolytic anemia, thrombocytopenia, hepatitis, nephritis, acute renal failure, and shock. These reactions are believed to be hypersensitivity reactions and related to antirifampin antibodies. Rifampin is also a potent inducer of hepatic microsomal enzymes. Its administration may result in decreasing the half-life of numerous compounds.

Animal

Chronic exposure to rifampin results in similar toxicity as in humans.

Immunotoxicity

Rifampin has been found to have an immunosuppressive effect in some animals; however, this is not thought to be

clinically relevant in humans taking it therapeutically. Hypersensitivity reactions may lead to acute renal failure. These are associated with the formation of antibodies to rifampin.

Genotoxicity

There is no evidence of mutagenicity for rifampin in bacteria, *Drosophila melanogaster*, or mice. An increase in chromatid breaks was seen in whole blood cells treated *in vitro* with rifampin. Rifampin increased the incidence of sister chromatid exchange in mouse bone marrow cells *in vitro* and increased the frequency of chromosomal aberrations in mouse spermatocytes.

Reproductive Toxicity

Rodents given high doses of rifampin (150–250 mg kg⁻¹ per day) had congenital malformations. Malformation and death in infants born to human mothers exposed to rifampin during their pregnancy occur at the same rates as the general population. Postnasal hemorrhage in mother and infant following administration of rifampin during the last few weeks of pregnancy has been rarely reported. Teratogenic effects including increased rates of cleft palate and spina bifida have been seen in rodents treated with 100–150 mg kg⁻¹ by bodyweight everyday with rifampin. Rifampin is not listed as a California Proposition 65 developmental or reproductive toxin nor is it listed as a United States Toxic Release Inventory (US TRI) developmental or reproductive toxin.

Carcinogenicity

In one report in which rifampin was used for 2 years to treat Pott's disease (tuberculosis of the spine), nasopharyngeal lymphoma was developed. In female mice an increase in hepatomas was seen following 1 year of administration at 2–10% of the maximum human dose. No evaluation of the carcinogenicity of rifampin in humans has been made. Rifampin is not listed on the California Proposition 65 list of known carcinogens nor is it listed on the United States Environmental Protection Agency list of carcinogens.

Clinical Management

Acute overdoses of rifampin are rarely serious. Good supportive care, gastric decontamination, and activated charcoal are all usually necessary. Given the extensive enterohepatic circulation of rifampin, repeated doses of activated charcoal may enhance elimination. Systemic toxicity associated with the chronic administration of rifampin is an indication to discontinue the drug.

See also: Poisoning Emergencies in Humans.

Further Reading

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Relevant Websites

- <http://www.inchem.org/documents/pims/pharm/rifam.htm#SectionTitle:1.3> – Inchem website on the chemical, pharmacologic and toxicologic properties of rifampin.
- <http://pubchem.ncbi.nlm.nih.gov> – US National Library of Medicine (Pubchem): Search for Rifampin.
- <http://img.thebody.com/nih/prof/rifampin.pdf> – Rifampin – Aids info (from the United States Department of Health and Human Services).
- http://www.pesticideinfo.org/Detail_Chemical.jsp?Rec_Id=PC42346 – Rifampin – PAN (Pesticides Database – chemicals).