Rifampicine

CAS: 13292-46-1
MF: C43-H58-N4-O12
MW: 822.94
log Kow= 4.24
Solubility: Freely soluble in chloroform and methyl chloride, dimethyl sulfoxide; soluble in tetrahydrofuran, ethyl acetate and methanol; slightly soluble in water (pH less than 6), acetone, carbon tetrachloride [1].

Major use
Rifampicine is an antibacterial drug, antibiotic, mainly used for the treatment of tuberculosis and leprosy [3].

Human toxicity
Acute overdosage of 10 g rifampicine in adults will usually elicit the "Red Man Syndrome": a brownish-red to orange discoloration of the skin, saliva, tears, sweat, urine, and feces. Color changes are reversible. Patients typically present with nausea, vomiting, mental status changes, and reddish discoloration of the skin following rifampicine antibiotic poisoning. Overdosage can rarely result in seizures, dysrhythmias, pulmonary edema and death [2].

Symptoms begin 30 to 240 minutes after ingestion and last up to 72 hours. Hepatitis and jaundice may be noted following chronic therapeutic administration of rifampicine and is most notable in patients with chronic liver disease, alcoholism, and old age [2].

The typical therapeutic rifampicin oral dose for adults is 600 mg once daily. The minimum lethal or toxic dose is not well established in the literature. Severity of intoxication must be based on clinical findings. Fatalities have been reported in adults ingesting 12 to 60 g. Some authors note that rifampicine may cause fatal intoxications especially in patients with hepatic dysfunction, alcohol abuse or lack of previous rifampicine treatment [2].

Peak plasma levels after a single therapeutic dose (10 mg/kg) range from 7 to 12 mg/l. The peak rifampicine level was 400 mg/l at 12 hours after ingestion of 12 g by an adult [2, 3].

Kinetic data
Absorption: 90% bioavailability [2]

Volume of distribution: 1-1.6 liters/kg [2, 3]. Rifampicine readily diffuses into most organs, tissues, bone and body fluids [3].

The plasma half-life: 2.1 hours; may be up to 4 to 5 hours in overdose [2].

Time to peak: 2 to 4 hours [2]

Protein binding: 60-89% [2, 3]

Metabolism and excretion

Rifampicine is deacetylated by the liver and eliminated by the biliary tract (70%) and urine (20%). Unchanged rifampicin undergoes enterohepatic circulation which prolongs its presence in the blood. Rifampicine is a potent inducer of the hepatic microsomal enzyme system [2].

The deacetylated derivative (desacetylrifampicine) of rifampicine is only slightly less active against mycobacteria than rifampicine. The metabolite is more water soluble than rifampicine and undergoes extensive enterohepatic circulation with eventual GI elimination. 10% of antibacterial activity in urine is formylrifampicin [2].

Metabolites more toxic than rifampicin: none.

Excretion:
Renal elimination is 16%; clearance of rifampicine is 8.8 ml/kg/min.
Of the total rifampicine in the urine, 35% is in the form of parent compound, 62% as the desacetyl metabolite and 3% as the formyl metabolite [2].

Pharmacological mechanism
Rifampicine acts by selectively inhibiting bacterial DNA-dependent RNA polymerase of susceptible strains of mycobacteria and other microorganisms, but not in mammalian cells, thus suppressing the initiation of chain formation in RNA synthesis [2].

Toxicological mechanisms
A proposed mechanism(s) for the development of rifampicine-induced thrombocytopenia and hemolysis is reactive metabolite(s) and/or rifampicine metabolites (e.g., desacetylrifampicine and/or formylrifampicine) covalently linking to host blood cell proteins, forming hapten-protein conjugates. The cell membrane is consequently damaged by the anti-drug antibody. Also, a cytotoxic response against blood cells may occur in response to the aberrant expression of hapten-conjugate on cellular membranes in conjunction with major histocompatibility complex I molecules. This may give rise to rifampicine-induced immune hemolytic anemia, intravascular hemolysis, hemoglobinuria and/or thrombocytopenia. Rifampicine-associated IgG antibodies may be generated [2].

Target organ: liver.

References

1. HSDB, TOXNET (2005).
2. Poisindex, Thomson Micromedex (2005).
3. Dollery, C., ed. (1993) *Therapeutic drugs*, Vols. 1 & 2. London: Churchill Livingstone.

Written by Cecilia Clemedson, November 2005, Cecilia@Stifud.se