

**Products: RH 150/100-B, RH 150/150-B, RH 150/75-B, RH 150/100, RH 300/150,
RH 150/150, RH 150/75**

RIFAMPICIN in combination with Isoniazid

Uses:

Tuberculosis as combination therapy

Contraindications and Precautions

Preparation not suitable for use in children

See also the separate monographs for Isoniazid and Rifampicin below

Dose:

Tuberculosis, 6-month regimen as combination therapy

By mouth:

Adult: 10 mg/kg (rifampicin) and 5 mg/kg (isoniazid) daily

Adult: 10 mg/kg (rifampicin) and 10 mg/kg (isoniazid) 3 times a week

RIFAMPICIN

General information

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic that inhibits ribonucleic acid synthesis in a broad range of microbial pathogens. It has bactericidal action and a potent sterilizing effect against tubercle bacilli in both cellular and extracellular locations. Rifampicin is lipid-soluble. Following oral administration, it is rapidly absorbed and distributed throughout the cellular tissues and body fluids; if the meninges are inflamed, significant amounts enter the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/ml in two to four hours, which subsequently decays with a half-life of two to three hours. It is extensively recycled in the enterohepatic circulation, and metabolites formed by deacetylation in the liver are eventually excreted in the faeces.

Since resistance readily develops, rifampicin must always be administered in combination with other effective antimycobacterial agents.

Clinical information

Uses

A component of all six and eight month anti-TB chemotherapeutic regimens currently recommended by WHO;

Leprosy

Dosage and administration

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food.

Rifampicin should be given as combination therapy

Adults and children: 10 mg/kg daily, *or* 2 or 3 times weekly (maximum dose, 600 mg daily)

Contraindications

- Known hypersensitivity to rifamycins
- Jaundice

Precautions

Serious immunological reactions resulting in renal impairment, haemolysis or thrombocytopenia are on record in patients who resume taking rifampicin after a prolonged lapse of treatment. In this rare situation it should be immediately and definitely withdrawn.

Careful monitoring of liver function is required in the elderly, and in patients who are alcohol-dependent, have hepatic disease or are on prolonged therapy.

Reduce dose in renal impairment.

Patients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputum, and that contact lenses may be irreversibly stained.

Patients or their care-givers should be told how to recognise signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

Use in pregnancy

Whenever possible, the six month regimen based upon isoniazid, rifampicin and pyrazinamide should be used.

Vitamin K should be administered to the infant at birth because of the risk of postnatal haemorrhage.

Adverse effects

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal tolerance can be unacceptably severe. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration. Exfoliative dermatitis is more frequent in HIV-positive TB patients. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported in patients taking the drug three times weekly. These reactions usually subside if the regimen is changed to one with daily dosage.

Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical significance. However, dose-related hepatitis can occur which is potentially fatal. It is consequently important not to exceed the maximum recommended daily dose of 10 mg/kg (600 mg).

Drug interactions

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroid contraceptives, oral hypoglycaemic agents, oral anticoagulants, phenytoin, cimetidine, cyclosporin and digitalis glycosides. Since rifampicin reduces the effectiveness of the oral contraceptive pill, women should consequently be advised to choose between one of the following two options for contraception. Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of oestrogen (50mcg). Alternatively she could use a nonhormonal

method of contraception throughout rifampicin treatment and for at least one month subsequently.

ISONIAZID

General information

Isoniazid, the hydrazide of isonicotinic acid is highly bactericidal against replicating tubercle bacilli.

It is rapidly absorbed and diffuses readily into all fluids and tissues. The plasma half-life, which is genetically determined, varies from less than one hour in fast acetylators to more than three hours in slow acetylators. It is largely excreted in the urine within 24 hours, mostly as inactive metabolites.

Clinical information

Uses

Tuberculosis treatment, in combination with other drugs

Tuberculosis prophylaxis and occasionally to prevent:

- transmission to close contacts at high risk of disease
- progression of infection to primary complex in recently infected, asymptomatic individuals
- recrudescence of infection in immunodeficient individuals.

Dosage and administration

By mouth, ADULT and CHILD

- 5 mg/kg (4–6 mg/kg) daily (maximum, 300 mg daily)
- *or* 10 mg/kg 3 times weekly
- *or* 15 mg/kg twice weekly

Tuberculosis, treatment in critically ill patients unable to take oral therapy (combination therapy), *use intramuscular injection*, **ADULT** 200–300 mg as single daily dose; **CHILD** 10–20 mg/kg daily

Tuberculosis, prophylaxis, *by mouth*

- **ADULT** 300 mg daily for at least 6 months
- **CHILD** 5 mg/kg daily for at least 6 months

Note: Isoniazid should be taken on an empty stomach; if taken with food to reduce gastrointestinal irritation, oral absorption and bioavailability may be impaired

Contraindications

- Known hypersensitivity
- Drug induced hepatic disease

Precautions

- Hepatic impairment (monitor hepatic function)
- Malnutrition
- Chronic alcohol dependence
- Chronic renal failure
- Diabetes mellitus

- HIV infection—prophylactic pyridoxine 10 mg daily required because risk of peripheral neuritis
- Epilepsy (isoniazid may provoke attacks)
- Slow acetylator status (increased risk of adverse effects)
- History of psychosis
- Pregnancy
- Breast-feeding
- Porphyria

Note: Patients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence or diabetes should additionally receive pyridoxine, 10 mg daily.

Note: For liver disorders, patients or their care-givers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as nausea, vomiting, malaise or jaundice develop

Adverse effects

Isoniazid is generally well tolerated at recommended doses. Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.

The risk of peripheral neuropathy is excluded if vulnerable patients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, including optic neuritis, toxic psychosis and generalized convulsions, can develop in susceptible individuals, particularly in the later stages of treatment and occasionally necessitate the withdrawal of isoniazid.

Hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is not of clinical significance, and usually resolves spontaneously during continuation of treatment.

Drug interactions

Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver. The absorption of isoniazid is impaired by aluminium hydroxide.

Overdosage

Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to three hours of overdosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of value.

Administration of high doses of pyridoxine is necessary to prevent peripheral neuritis.

Storage

Tablets should be kept in well-closed containers, protected from light. Solution of injection should be stored in ampoules protected from light.