TREATMENT OF TUBERCULOSIS

Annex 6

ESSENTIAL FIRST-LINE ANTITUBERCULOSIS DRUGS

2017 UPDATE

World Health Organization

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Contents

Note

For drug preparations (include fixed-dose combinations) and costs, see the Global Drug Facility web site: www.stoptb.org/gdf/drugsupply/drugs_available.asp.

See also WHO Model Formulary 2017: http://www.who.int/selection_medicines/list/en

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 1 hour in fast acetylators to more than 3 hours in slow acetylators. Isoniazid is largely excreted in the urine within 24 hours, mostly as inactive metabolites.

Clinical information

Administration and dosage

Isoniazid is normally taken orally but may be administered intramuscularly or intra¬venously to critically ill patients.

Adults:
5 mg/kg (4–6 mg/kg) daily

Contraindications

- Known hypersensitivity.
- Active, unstable hepatic disease (with jaundice)

Precautions

Clinical monitoring (and liver function tests, if possible) should be performed dur¬ing treatment of patients with pre-existing liver disease. Patients at risk of peripheral neuropathy, as a result of malnutrition, chronic alcohol dependence, HIV infection, pregnancy, breastfeeding, renal failure or diabetes, should additionally receive pyri¬doxine, 10 mg daily. Where the standard of health in the community is low, pyridox¬ine should be offered routinely. For established peripheral neuropathy, pyridoxine should be given at a dose of 50–75 mg daily.

Since isoniazid interacts with anticonvulsants used for epilepsy, it may be necessary to reduce the dosage of these drugs during treatment with isoniazid. If possible, se¬rum concentrations of phenytoin and carbamazepine should be measured in patients receiving isoniazid with or without rifampicin (see Drug interactions below).

Use in pregnancy

Isoniazid is not known to be harmful in pregnancy. Pyridoxine supplementation is recommended for all pregnant (or breastfeeding) women taking isoniazid.

Adverse effects

Isoniazid is generally well tolerated at recommended doses.

Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment.

Sleepiness or lethargy can be managed by reassurance or adjustment of the timing of administration.

The risk of peripheral neuropathy is excluded if vulnerable patients receive daily supplements of pyridoxine. Other less common forms of neurological disturbance, in¬cluding 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.

Symptomatic hepatitis is an uncommon but potentially serious reaction that can usually be averted by prompt withdrawal of treatment. More often, however, an asymptomatic rise in serum concentrations of hepatic transaminases at the outset of treatment is of no clinical significance and usually resolves spontaneously as treat¬ment continues.

A lupus-like syndrome, pellagra, anaemia, and arthralgias are other rare adverse ef¬fects. Monoamine poisoning has been reported to occur after ingestion of foods and beverages with high monoamine content, but this is also rare.

Drug interactions

Isoniazid inhibits the metabolism of certain drugs, which can increase their plasma concentration to the point of toxicity. Rifampicin, however, has the opposite effect for many of these drugs. For example, the available data indicate that administering both rifampicin and isoniazid causes a reduction in plasma levels of phenytoin and diazepam.

Isoniazid may increase the toxicity of carbamazepine, benzodiazepines metabolized by oxidation (such as triazolam), acetaminophen, valproate, serotonergic antidepres¬sants, disulfiram, warfarin and theophylline.

Overdosage

Nausea, vomiting, dizziness, blurred vision and slurring of speech occur within 30 minutes to 3 hours of overdosage. Massive poisoning results in coma preceded by respiratory depression and stupor. Severe intractable seizures may occur. Emesis and gastric lavage, activated charcoal, antiepileptics and IV sodium bicarbonate can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of value. High doses of pyridoxine must be administered to prevent seizures

Storage

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

Rifampicin

General information

A semisynthetic derivative of rifamycin, rifampicin is 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 600mg produces a peak serum concentration of about 10 µg/ml in 2–4 hours, which subsequently decays with a half-life of 2–3 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

Administration and dosage

Rifampicin should preferably be given at least 30 minutes before meals, since absorption is reduced when it is taken with food. However, this may not be clinically significant, and food can reduce intolerance to drugs. Rifampicin should always be given in combination with other effective antimycobacterial agents. It is also available for intravenous administration in critically ill patients.

Adults:
10 mg/kg (8–12 mg/kg) daily.

Contraindications

- Known hypersensitivity to rifamycins.
- Active, unstable hepatic disease (with 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, rifampicin should be immedi¬ately and permanently withdrawn.

Clinical monitoring (and liver function tests, if possible) should be performed during treatment of all patients with pre-existing liver disease, who are at increased risk of further liver damage.

Patients should be warned that treatment may cause reddish coloration of all body secretions (urine, tears, saliva, sweat, semen and sputum), and that contact lenses and clothing may be irreversibly stained.

Use in pregnancy

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

Adverse effects

Rifampicin is well tolerated by most patients at currently recommended doses but may cause gastrointestinal reactions (abdominal pain, nausea, vomiting) and pruri¬tus with or without rash.

Other adverse effects (fever, influenza-like syndrome and thrombocytopenia) are more likely to occur with intermittent administration.

Exfoliative dermatitis is more frequent in HIV-positive TB patients.

Moderate rises in serum concentrations of bilirubin and transaminases, which are common at the outset of treatment, are often transient and without clinical signifi¬cance. However, dose-related hepatitis can occur and is potentially fatal.

Drug interactions

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver, including:

- anti-infectives (including certain antiretroviral drugs discussed below, mefloquine, azole antifungal agents, clarithromycin, erythromy¬cin, doxycycline, atovaquone, chloramphenicol);
- hormone therapy, including ethinylestradiol, norethindrone, tamoxifen, levothyroxine;
- methadone;
- warfarin;
- cyclosporine;
- corticosteroids;
- anticonvulsants (including phenytoin);
- cardiovascular agents including digoxin (in patients with renal insufficiency), digitoxin, verapamil, nifedipine, diltiazem, propranolol, metoprorol, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone;
- theophylline;
- sulfonylurea hypoglycaemics;
- hypolipidaemics including simvastatin and fluvastatin;
- nortriptyline, haloperidol, quetiapine, benzodiazepines (including diazepam, triazolam), zolpidem, buspirone.

Since rifampicin reduces the effectiveness of oral contraceptives, women should be advised to choose between one of two options for contraception. Following consul¬tation with a clinician, the patient may use an oral contraceptive pill containing a higher dose of estrogen (50 µg); alternatively, a non hormonal method of contracep¬tion may be used throughout rifampicin treatment and for at least one month sub¬sequently.

Biliary excretion of radiocontrast media and sulfobromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B12 disturbed.

Overdosage

Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses of rifampicin may depress central nervous function. There is no specific antidote and treatment is supportive.

Storage

Capsules and tablets should be kept in tightly closed containers, protected from light.

Pyrazinamide

General information

Pyrazinamide is a synthetic analogue of nicotinamide that is only weakly bactericidal against M. tuberculosis but has potent sterilizing activity, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation. It is highly effective during the first 2 months of treatment while acute inflammatory changes persist. Its use has enabled treatment regimens to be shortened and the risk of relapse to be reduced.

It is readily absorbed from the gastrointestinal tract and is rapidly distributed throughout all tissues and fluids. Peak plasma concentrations are attained in 2 hours and the plasma half-life is about 10 hours. It is metabolized mainly in the liver and excreted largely in the urine.

Clinical information

Administration and dosage

Pyrazinamide is administered orally.

Adults (usually for the first 2 or 3 months of TB treatment):
25 mg/kg (20–30 mg/kg) daily

Contraindications

- Known hypersensitivity.
- Active, unstable hepatic disease (with jaundice).
- Porphyria.

Precautions

Patients with diabetes should be carefully monitored since blood glucose concentra¬tions may become labile. Gout may be exacerbated. Clinical monitoring (and liver function tests, if possible) should be performed during treatment of patients with pre-existing liver disease.

Use in pregnancy

The 6-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used whenever possible. Although detailed teratogenicity data are not available, pyrazinamide can probably be used safely during pregnancy.

Adverse effects

Pyrazinamide may cause gastrointestinal intolerance.

Hypersensitivity reactions are rare, but some patients complain of slight flushing of the skin.

Moderate rises in serum transaminase concentrations are common during the early phases of treatment. Severe hepatotoxicity is rare.

As a result of inhibition of renal tubular secretion, a degree of hyperuricaemia usu¬ally occurs, but this is often asymptomatic. Gout requiring treatment with allopuri¬nol occasionally develops. Arthralgia, particularly of the shoulders, may occur and is responsive to simple analgesics (especially aspirin). Rare adverse events include sideroblastic anaemia and photosensitive dermatitis.

Overdosage

Little has been recorded on the management of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially sympto¬matic. Emesis and gastric lavage may be of value if undertaken within a few hours of ingestion. There is no specific antidote and treatment is supportive.

Storage

Tablets should be stored in tightly closed containers, protected from light.

Ethambutol

General information

A synthetic congener of 1,2-ethanediamine, ethambutol is active against M. tuber¬culosis, M. bovis and some nonspecific mycobacteria. It is used in combination with other anti-TB drugs to prevent or delay the emergence of resistant strains.

It is readily absorbed from the gastrointestinal tract. Plasma concentrations peak in 2–4 hours and decay with a half-life of 3–4 hours. Ethambutol is excreted in the urine both unchanged and as inactive hepatic metabolites. About 20% is excreted unchanged in the faeces.

Clinical information

Administration and dosage

Ethambutol is administered orally.

Adults:
15 mg/kg (15–20 mg/kg) daily

Dosage must always be carefully calculated on a weight basis to avoid toxicity, and the dose or the dosing interval should be adjusted in patients with impaired renal function (creatinine clearance <70 ml/min).

Contraindications

- Known hypersensitivity.
- Pre-existing optic neuritis from any cause.

Precautions

Patients should be advised to discontinue treatment immediately and to report to a clinician if their sight or perception of colour deteriorates. Ocular examination is recommended before and during treatment. Whenever possible, renal function should be assessed before treatment. Plasma ethambutol concentration should be monitored if creatinine clearance is less than 30 ml/min.

Use in pregnancy

Ethambutol is not known to be harmful in pregnancy.

Adverse effects

Dose-dependent optic neuritis can result in impairment of visual acuity and colour vision in one or both eyes. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Ocular toxicity is rare when etham¬butol is used for 2–3 months at recommended doses.

Signs of peripheral neuritis occasionally develop in the legs.

Other rare adverse events include generalized cutaneous reaction, arthralgia and, very rarely, hepatitis.

Overdosage

Emesis and gastric lavage may be of value if undertaken within a few hours of inges¬tion. Subsequently, dialysis may be of value. There is no specific antidote and treat¬ment is supportive.

Storage

Tablets should be stored in tightly closed containers.

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