

Essential Drugs

WHO Model Formulary

As described in previous issues of this journal, work is now under way on the WHO Model Formulary, and draft texts will be published regularly to obtain comments on the material proposed for publication. Observations concerning the following sections should be addressed to: Drug Selection and Information (DSI), Division of Drug Management & Policies, World Health Organization, 1211 Geneva 27, Switzerland.

Antibacterials Antileprosy drugs

Leprosy is a chronic mycobacterial infection which affects people of all ages and both sexes. Paucibacillary and multibacillary leprosy are the two clinical forms of the disease. Single-lesion leprosy is a form of paucibacillary leprosy.

In paucibacillary (PB) leprosy, peripheral nerve involvement may result in no more than minor, localized impairment of sensation but, in severe cases, extensive sensory and motor loss can induce trophic changes, muscle wasting and contractures. In multibacillary (MB) leprosy, nerve damage commonly occurs and, if left untreated, may lead to crippling deformities. Visual impairment or blindness is a frequent complication in both paucibacillary and multibacillary leprosy.

Dapsone, which is bacteriostatic or weakly bactericidal against *Mycobacterium leprae*, was the mainstay of treatment for leprosy for many years until widespread resistant strains appeared. Combination therapy has become essential to prevent the emergence of resistance. **Rifampicin** is now combined with **dapsone** to treat PB leprosy and **rifampicin** and **clofazimine** are now combined with **dapsone** to treat MB leprosy. The WHO Action Programme for the Elimination of Leprosy currently provides oral multidrug therapy (MDT) in blister packs which ensure better patient compliance. More recently, a one-time dose of combination therapy has been recommended to cure patients with single-skin-lesion leprosy. (WHO-recommended treatment regimens are set out in the tables on page 254).

Any patient with a positive skin smear should be treated with the MDT regimen for multibacillary leprosy. Never give the regimen for paucibacillary leprosy to a patient with multibacillary leprosy. If diagnosis in a particular patient is not possible, treat that patient with the MDT regimen for multibacillary leprosy.

Lepra reactions are episodes of sudden increase in the activity of leprosy and are often accompanied by neuritis. Reactions must always be treated promptly to prevent permanent nerve damage and disability. During a lepra reaction, continue giving leprosy multidrug therapy without interruption. This will reduce the frequency and severity of lepra reactions.

Type I lepra reactions, or reversal reactions, are delayed hypersensitivity reactions and may occur in either paucibacillary or multibacillary leprosy. If there is no nerve damage, treat type I reactions with analgesics, such as acetylsalicylic acid or paracetamol. If there is nerve involvement use corticosteroids, such as oral prednisolone.

The type II lepra reaction, also known as erythema nodosum leprosum (ENL), is an antibody response to dead leprosy bacteria and occurs only in multibacillary leprosy. Therapy for type II reactions may include analgesics, such as acetylsalicylic acid or paracetamol, and corticosteroids, such as oral prednisolone. In patients not responding to corticosteroids, thalidomide or clofazimine may be used under close medical supervision. Thalidomide should be avoided in women of childbearing age since it is a proven teratogen. If this is not possible, it is imperative that pregnancy is excluded before this treatment is initiated. Effective contraception

WHO-recommended treatment regimens

Single-lesion paucibacillary (PB) leprosy					
one-time dose of 3 medications taken together					
	<i>Rifampicin</i>	<i>Ofloxacin</i>	<i>Minocycline</i>		
Adult 50–70 kg	600 mg	400 mg	100 mg		
Child 5–14 years ^a	300 mg	200 mg	50 mg		
^a Adjust dose appropriately for child less than 5 years					
6-month regimen for paucibacillary (PB) leprosy					
	<i>Dapsone</i>		<i>Rifampicin</i>		
Adult 50–70 kg	100 mg given daily		600 mg given once a month, under supervision		
Child 10–14 years ^b	50 mg given daily		450 mg given once a month, under supervision		
^b Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily and rifampicin 300 mg given once a month under supervision					
12-month regimen for multibacillary (MB) leprosy					
	<i>Dapsone</i>	<i>Rifampicin</i>	<i>Clofazimine</i>		
Adult 50–70 kg	100 mg given daily	600 mg given once a month under supervision	50 mg given daily	<u>and</u>	300 mg given once a month under supervision
Child 10–14 years ^c	50 mg given daily	450 mg given once a month under supervision	50 mg given every other day	<u>and</u>	150 mg given once a month under supervision
^c Adjust dose appropriately for child less than 10 years. For example, dapsone 25 mg daily, rifampicin 300 mg given once a month under supervision, clofazimine, 50 mg given twice a week, and clofazimine 100 mg given once a month under supervision					

must be used during the 4 weeks preceding and following treatment as well as during the treatment period. Should pregnancy occur despite these precautions, there is a high risk of severe malformation of the fetus.

If a patient does not respond to lepra reaction treatment within 6 weeks or seems to become worse, the patient must be sent immediately to the nearest specialist centre.

Combination therapy prevents the development of drug resistance. Experience with multidrug therapy has shown that adverse effects do not occur often and relapses are rare.

CLOFAZIMINE

Capsule: 50 mg, 100 mg

Uses: Multibacillary leprosy in combination with dapsone and rifampicin. For type II lepra reactions, as an alternative or in addition to analgesics, corticosteroids or thalidomide.

Dosage:

Multibacillary leprosy (in combination with dapsone and rifampicin)

Adults: 50 mg daily for 12 months, AND 300 mg once a month, supervised.

Children 10–14 years of age: 50 mg given on alternate days for 12 months, AND 150 mg once a month, supervised.

Children under 10 years of age: Adjust the dose. For example, 50 mg twice a week for 12 months AND 100 mg once a month, supervised.

Erythema nodosum leprosum (type II lepra reactions)

Adults and children: 200–300 mg daily in 2 or 3 divided doses. 4–6 weeks may be needed before an effect is seen. Hospitalize a patient with severe type II lepra reactions for supervised medical care.

Precautions: Patients with pre-existing gastrointestinal disease require medical supervision. Liver function and creatinine clearance should be monitored.

Adverse effects: Reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine may occur. Dose-related gastrointestinal symptoms include pain, nausea, vomiting and diarrhoea. Prolonged treatment with high doses may cause rare but severe mucosal and submucosal oedema, severe enough to produce symptoms of subacute small-bowel obstruction needing supervised medical care.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

DAPSONE

Tablet: 25 mg, 50 mg, 100 mg

Uses: Paucibacillary and multibacillary leprosy in combination with other antileprosy drugs.

Dosage:

Paucibacillary leprosy (in combination with rifampicin)

Adults: 100 mg daily for 6 months.

Children 10–14 years of age: 50 mg daily for 6 months.

Children under 10 years of age: Adjust the dose. For example, 25 mg daily for 6 months.

Multibacillary leprosy (in combination with rifampicin and clofazimine)

Adults: 100 mg daily for 12 months

Children 10–14 years of age: 50 mg daily for 12 months.

Children under 10 years of age: Adjust the dose. For example, 25 mg daily for 12 months

Contraindications: Known hypersensitivity to sulfones; severe anaemia.

Precautions: Treat pre-existing severe anaemia before therapy. Dapsone can induce haemolysis, particularly in glucose-6-phosphate dehydrogenase deficiency, and can cause dose-dependent methaemoglobinaemia. These adverse effects are seen early in therapy. Monitor clinical response and blood count in susceptible patients during first weeks of treatment.

Adverse effects: Varying degrees of dose-related haemolysis and methaemoglobinaemia are the most frequently reported adverse effects. A "dapsone syndrome", which resembles mononucleosis is a rare hypersensitivity reaction. Symptoms include skin rash, fever, jaundice and eosinophilia. Occasionally, gastrointestinal irritation is reported and, uncommonly, headache, nervousness and insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy, psychoses. Rarely, hepatitis and agranulocytosis occur.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

RIFAMPICIN

Capsule or tablet 150 mg, 300 mg

Uses: Paucibacillary and multibacillary leprosy in combination with other antileprosy drugs.

Dosage:

Paucibacillary leprosy (in combination with dapsone).

Adults: 600 mg, supervised, once a month for 6 months.

Children 10–14 years of age: 450 mg, supervised, once a month for 6 months.

Children under 10 years of age: Adjust the dose. For example, 300 mg, supervised, once a month for 6 months.

Multibacillary leprosy (in combination with dapsone and clofazimine)

Adults: 600 mg, supervised, once a month for 12 months.

Children 10–14 years of age: 450 mg, supervised, once a month for 12 months.

Children under 10 years: Adjust the dose. For example, 300 mg, supervised, once a month for 12 months.

Contraindications: Hepatic dysfunction.

Precautions: Patients who resume taking rifampicin after a long interval may have serious immunological reactions, resulting in renal impairment, haemolysis, or thrombocytopenia. In this rare situation, stop rifampicin immediately. Never give rifampicin again to this patient.

Monitor liver function in the elderly, in patients who are alcohol-dependent and in patients with hepatic disease. Rifampicin produces a red colour in urine, tears, saliva and sputum and may stain contact lenses permanently.

Adverse effects: In some patients, severe gastrointestinal disturbances may occur. Skin rashes, fever, influenza-like syndrome and thrombocytopenia are more likely to occur during intermittent therapy.

Moderate rises in serum concentrations of bilirubin and transaminases often occur at the start of treatment, are often transient and do not have clinical significance.

Do not exceed the maximum recommended daily dose of 600 mg since potentially fatal, dose-related hepatitis may occur.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary. Advise women taking oral contraceptives to use nonsteroidal forms of contraception.

MINOCYCLINE

Tablet, 50 mg, 100 mg

Uses: Single-skin-lesion paucibacillary leprosy, in combination with rifampicin and ofloxacin.

Dosage:

Adults: Single dose of 100 mg.

Children over 8 years of age: Single dose of 50 mg.

Contraindications: Children under 8 years of age, since skeletal deposition can result in retardation of bone growth, hypoplasia of dental enamel and permanent brown discoloration of teeth.

Precautions: Monitor liver function prior to administration. Patient should avoid exposure to sunlight. Do not give with iron salts or with antacids containing calcium, magnesium or aluminium.

Adverse effects: Vestibular disturbances causing dizziness and vertigo are more common in women than in men. Gastrointestinal effects such as nausea, vomiting, and diarrhoea may occur. Headache or visual disturbances may indicate intracranial hypertension.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

OFLOXACIN

Tablets, 200 mg, 400 mg

Uses: Single-skin-lesion paucibacillary leprosy in combination with rifampicin and minocycline.

Dosage:

Adults: A single dose of 400 mg.

Children: A single dose of 200 mg.

Precautions: Use with extreme caution in patients with epilepsy, a history of epilepsy or a history of central nervous system disorders. Impaired renal or hepatic function. Avoid exposure to sunlight. Wait at least 4 hours before giving any product containing aluminium, iron or magnesium salts. Give with a full (250 ml) glass of water.

Adverse effects: May induce convulsions in patients with or without a history of convulsions. Nausea, vomiting, abdominal pain, diarrhoea, headache, visual disturbances, sleep disorders, rash, pruritus, and fever are frequently reported.

Drug interactions: Taking nonsteroidal anti-inflammatory drugs with ofloxacin may induce convulsions. Other drug interactions will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

Antibacterials

Antituberculosis drugs

Tuberculosis is the most prevalent infectious disease of adults and causes 26% of avoidable adult deaths in the developing world. More than 80% of tuberculosis cases are pulmonary (PTB). At least 30% of patients who are infected with HIV will also develop active tuberculosis. Left untreated, 50% of tuberculosis patients die within 5 years and most of the surviving patients with tuberculosis will be seriously debilitated. All patients represent a source of infection to others.

The essential tools against tuberculosis are detection and treatment, with priority given to infectious cases. Short-course therapy which lasts for 6 or 8 months, given under direct observation (DOTS), is one of the most important components of the WHO strategy against tuberculosis. Active tuberculosis, no matter how mild, must never be treated with a single drug because of the risk of acquired resistance.

The 6 antituberculosis drugs, **isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol and thioacetazone**, are used in various combinations as part of the WHO recommended treatment regimens set out in the table on page 258.

In countries with a high incidence of tuberculosis, routine **drug susceptibility testing** is not recommended and is not normally feasible for all patients. Drug susceptibility tests should be conducted only if the reliability and consistency of the results can be guaranteed by careful standardization and quality control.

In clinics where culture facilities and reliable drug susceptibility testing are available, testing may be useful in cases of treatment failure or relapse or for chronic cases. Testing should be used only after

failure of standardized chemotherapy, given as DOTS, and should be used to assist in decision-making regarding the future therapy of a particular patient.

A change of drug regimen should be considered only if the patient fails to respond after 5 months of DOTS. Poor compliance is a far more common reason for failure of chemotherapy than is drug resistance. Alternative therapy, as set out in the table on page 259, may be administered as specified.

Worldwide, an important predisposing cause of immunosuppression leading to tuberculosis is **human immunodeficiency virus (HIV) infection** which increases the reactivation rate of tuberculosis. Preventive antituberculosis therapy of such persons is recommended.

Fixed-dose combination (FDC) tablets incorporate two or more drugs within the same dosage form. Use of single antituberculosis drugs increases the risk of emergence of drug-resistant organisms. FDCs provide a more effective regimen, decrease inadvertent medication errors and improve compliance.

Where the disease remains highly prevalent, routine **immunization** of infants within the first year of age with BCG vaccine is cost-effective. However, there is no evidence that BCG will protect children older than 15 years of age. Infants born to HIV-positive mothers should be vaccinated during the first year of life, provided they have no clinical signs suggestive of HIV.

Chemoprophylaxis with isoniazid can prevent the development of clinically apparent disease in persons in close contact with infectious patients, and in other persons at high risk. In countries with high tuberculosis prevalence, the recommended policy is to give isoniazid for at least 6 months to any child under 5 years of age who is in close contact with an infectious case of tuberculosis, provided the child is apparently healthy and does not have any symptoms of tuberculosis. Do not consider the BCG status of that child. In some countries or in populations with a high HIV prevalence, it is strongly recommended that chemoprophylaxis is given to patients who are HIV-positive and are also tuberculin positive.

The **tuberculin test** has limited diagnostic value. A positive tuberculin test indicates previous exposure

WHO recommended treatment regimen for tuberculosis^a

6-month regimen		
Drug	Phase 1: 2 months	Phase 2: 4 months
isoniazid	5 mg/kg daily	5 mg/kg daily
rifampicin	10 mg/kg daily	10 mg/kg daily
pyrazinamide	25 mg/kg daily	
<i>together with</i>		
streptomycin	15 mg/kg daily	
<i>or</i>		
ethambutol	15 mg/kg daily ^b	
<i>OR</i>		
isoniazid	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
rifampicin	10 mg/kg 3 times weekly	10 mg/kg 3 times weekly
pyrazinamide	35 mg/kg 3 times weekly	
<i>together with</i>		
streptomycin	15 mg/kg 3 times weekly	
<i>or</i>		
ethambutol	30 mg/kg 3 times weekly ^b	
8-month regimen		
Drug	Phase 1: 2 months	Phase 2: 6 months
isoniazid	5 mg/kg daily	5 mg/kg daily
rifampicin	10 mg/kg daily	
pyrazinamide	30 mg/kg daily	
thioacetazone		2.5 mg/kg daily
<i>together with</i>		
streptomycin	15 mg/kg daily	
<i>or</i>		
ethambutol	25 mg/kg daily ^b	25 mg/kg daily ^b
^a Unless otherwise indicated, doses are suitable for both adults and children.		
^b Not suitable for children.		

to mycobacterial antigens through infection with one of the tubercle bacilli, or BCG vaccination. The tuberculin test does not distinguish between tuberculosis and other mycobacterial infection, between active and quiescent disease, or between acquired infection and seroconversion induced by BCG vaccination.

ISONIAZID

Tablet: 100, 300 mg

Injection: 25 mg/ml in 2-ml ampoule

Uses: A component of all combined antituberculosis regimens currently recommended by WHO. Occasionally used alone to prevent transmission to close contacts or others at high risk and to prevent progression of infection in recently infected,

asymptomatic individuals, particularly those who are immunodeficient.

Dosage: Normally taken by mouth, but may also be administered intramuscularly to critically ill patients.

Treatment (as WHO recommended regimen)

Adults and children: 5 mg/kg (4–6 mg/kg) daily – maximum 300 mg – or 10 mg/kg three times weekly or 15 mg/kg twice weekly.

Prophylaxis

Adults: 300 mg daily for at least 6 months.

Children: 5mg/kg for at least 6 months.

Contraindications: Active hepatic disease.

Precautions: Monitor hepatic function since isoniazid is associated with liver toxicity. Monitor serum concentrations of hepatic transaminases which indicate an increase in liver enzymes. If

Alternative treatment regimen

Treatment category	Alternative TB treatment regimens	
	Initial phase (daily or 3 times weekly)	Continuation phase
H= isoniazid, R= rifampicin, Z=pyrazinamide, E=ethambutol, S=streptomycin Dosage must be evaluated on an individual basis.		
1. New cases of smear-positive pulmonary tuberculosis (PTB) and new cases of smear-negative PTB with extensive parenchymal involvement. New cases of severe forms of extrapulmonary TB.	2 EHRZ (SHRZ) 2 EHRZ (SHRZ) 2 EHRZ (SHRZ)	6 HE 4 HR 4 H ₃ R ₃
2. Relapse. Sputum smear-positive cases previously treated. Treatment failure in smear-positive cases. Restart treatment after interruption.	2 SHRZE / 1 HRZE 2 SHRZE / 1 HRZE	5 H ₃ R ₃ E ₃ 5 HRE
3. New smear-negative PTB (other than in 1); new less severe forms of extrapulmonary TB.	2 HRZ 2 HRZ 2 HRZ	6 HE 4 HR 4 H ₃ R ₃
4. Chronic case (still smear-positive after supervised re-treatment)	See <i>Guidelines for the management of drug-resistant tuberculosis</i> , WHO/TB/96.210 (Rev. 1), WHO, 1997, and <i>Guidelines for national programmes</i> , WHO/TB/97.220.	
<i>N.B. Some authorities recommend a 7-month continuation phase with daily isoniazid and rifampicin (7HR) for category 1 patients with the following forms of TB: TB meningitis, miliary TB, spinal TB with neurological signs.</i>		
<i>A regimen consists of 2 phases, the initial phase and the continuation phase. The number before a phase is the duration of that phase in months. The number in subscript after a letter is the number of doses of that drug per week. If there is no number in subscript after a letter, then treatment with that drug is daily. An alternative drug(s) appears as a letter(s) in parentheses.</i>		

signs of liver disease appear, the patient must stop treatment and seek immediate medical attention. Patients at risk of peripheral neuropathy as a result of malnutrition, chronic alcohol dependence, chronic renal failure or diabetes should supplement their tuberculosis medication with pyridoxine (vitamin B₆), 10 mg daily. When the standard of health in the community is low, patients should routinely be given pyridoxine. Isoniazid may provoke epilepsy.

If taking an aluminium-containing antacid, wait at least 1 hour after taking isoniazid.

Adverse effects: Frequently produces gastrointestinal disturbances (nausea, diarrhoea, vomiting, stomach pain). To reduce gastrointestinal irritation, isoniazid should be taken with food, however, this may impair oral absorption and bioavailability.

Occasionally, systemic or cutaneous hypersensitivity during first weeks of treatment may be experienced. Risk of peripheral neuropathy is reduced if patients take pyridoxine. Other, less common, neurological disturbances including optic neuritis, toxic psychosis and generalized convulsions, particularly during the later stages of treatment may occur. Isoniazid withdrawal may be necessary. Hypersensitivity reactions include skin eruptions, skin rash, fever, and joint pain.

Hepatitis is uncommon but potentially serious and, when this occurs, isoniazid should be stopped. Hepatitis is seen more often in patients over 35 years of age and in regular drinkers of alcohol. Fatigue may indicate liver damage. Patients who inactivate isoniazid slowly (slow acetylators) tend to have a higher incidence of adverse effects, especially peripheral neuritis, and may require smaller doses.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

RIFAMPICIN

Capsule or tablet 150 mg, 300 mg

Uses: A component of all 6 and 8-month anti-tuberculosis regimens currently recommended by WHO.

Dosage:

Adults and children: 10 mg/kg daily or two or three times weekly. Maximum dose is 600 mg daily.

Give at least 30 minutes before meals since rifampicin absorption is reduced when taken with food.

Contraindications: Hepatic dysfunction.

Precautions: Patients who resume taking rifampicin after a long interval may have serious immunological reactions resulting in renal impairment, haemolysis, or thrombocytopenia. In this rare situation, stop rifampicin immediately. Never give rifampicin again to this patient.

Monitor liver function in the elderly, in patients who are alcohol-dependent and in patients with hepatic disease. Rifampicin produces a red colour in urine, tears, saliva and sputum and may stain contact lenses permanently.

Adverse effects: In some patients, severe gastrointestinal disturbances may occur. Skin rashes, fever, influenza-like syndrome and thrombocytopenia are more likely to occur during intermittent therapy. Exfoliative dermatitis is also observed in HIV-positive tuberculosis patients. Temporary oliguria, dyspnoea and haemolytic anaemia have been reported.

Moderate rises in serum concentrations of bilirubin and transaminases often occur at the start of treatment, are often transient and do not have clinical significance.

Do not exceed the maximum recommended daily dose of 600 mg since potentially fatal, dose-related hepatitis may occur.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary. Advise women taking oral contraceptives to use nonsteroidal forms of contraception.

RIFAMPICIN /ISONIAZID

Tablet: 150 mg rifampicin + 75 mg isoniazid, 300 mg rifampicin + 150 mg isoniazid, 150 mg rifampicin + 150 mg isoniazid

Uses: Both drugs are components of anti-tuberculosis regimens currently recommended by WHO.

Dosage: This fixed-dose combination tablet is reserved for phase 2 of the 6-month WHO treatment schedule (see table on page 258). The combination tablet is not suitable for children.

For daily use

Adults: Dose of 10 mg/kg rifampicin and 5 mg/kg isoniazid

For three times weekly use

Adults: Dose of 10 mg/kg rifampicin and 10 mg/kg isoniazid.

Contraindications, precautions, adverse effects and drug interactions: Refer to information given for each individual substance.

PYRAZINAMIDE

Tablet: 400 mg, 500 mg

Uses: A component of all 6- and 8-month anti-tuberculosis regimens currently recommended by WHO.

Dosage:

Adults and children: 25 mg/kg daily or 35 mg/kg three times weekly or 50 mg/kg twice weekly.

Contraindications: Known hypersensitivity; severe hepatic impairment.

Precautions: Monitor blood glucose carefully in diabetic patients since this may change suddenly. Gout may be exacerbated.

Adverse effects: Moderate rises in serum transaminase concentrations are common during early phases of treatment.

A degree of asymptomatic hyperuricaemia usually occurs. Arthralgia, particularly of the shoulders, is also common and can be treated with simple analgesics. Hyperuricaemia and arthralgia can be reduced by using regimens with intermittent administration of pyrazinamide. Gout requiring allopurinol treatment occasionally develops. Rarely, hypersensitivity is reported and some patients complain about skin flushing.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

STREPTOMYCIN

Powder for injection: 1 g (as sulfate) in vial

Uses: A component of several combined anti-tuberculosis regimens currently recommended by WHO.

Dosage: Administer streptomycin by deep intramuscular injection. Use only sterile needles and syringes.

Adults: 15 mg/kg daily or two or three times weekly. Patients over 60 years may not tolerate more than 500–750 mg daily.

Contraindications: Auditory nerve impairment; myasthenia gravis.

Precautions: If possible, do not use streptomycin in children since the injections are painful, and irreversible auditory nerve damage may occur. Wear protective gloves to avoid sensitization dermatitis.

Withdraw if hypersensitivity occurs (commonly, during the first week of treatment). Monitor plasma levels periodically in the elderly and in patients with renal impairment. Adjust streptomycin dose to avoid dose-related toxic effects resulting from drug accumulation. Adjust dose to ensure that plasma concentrations, measured at maximum trough concentrations (just before the next dose is due) do not rise above 4 µg/ml (4 mg/litre).

Adverse effects: Painful and sterile abscesses may form at injection sites. Hypersensitivity reactions are common and can be severe. Streptomycin may produce ototoxicity. Vestibular ototoxicity presents as clumsiness, dizziness, vertigo, nausea and unsteadiness. Auditory ototoxicity includes hearing loss or ringing, buzzing or a feeling of fullness in the ears. Streptomycin affects vestibular function more often than auditory function but impairment of vestibular function appears to be uncommon with currently recommended doses.

Streptomycin may produce nephrotoxicity. Close monitoring of renal function is required. Halve the dose if urinary output falls, if albuminuria is seen, or if urine has tubular casts. Rarely produces haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

ETHAMBUTOL

Tablet: 100 mg, 400 mg (hydrochloride)

Uses: An optional component of several combined antituberculosis regimens currently recommended by WHO.

Dosage: This must always be calculated on a weight basis to avoid toxicity, and should be reduced in patients with impaired renal function.

Adults: 15 mg/kg daily or 30 mg/kg three times weekly.

Contraindications: Pre-existing optic neuritis from any cause; inability to report symptomatic visual disturbances; creatinine clearance of less than 50 ml/minute.

Precautions: Ethambutol may damage the vision. Test vision before and regularly during administration. Ethambutol may produce optic neuritis, which causes eye pain, decreased visual acuity, general loss of vision, central and peripheral constriction of visual fields, and loss of red/green colour perception. If the patient has any indication that the perception of colour or the sight is deteriorating, treatment must be stopped immediately and the doctor consulted. Do not give ethambutol to any patient too young to understand this warning or who cannot communicate any visual problems.

Whenever possible, renal function should be assessed before and regularly during treatment. Ethambutol will have increased serum concentration and prolonged half-life in patients with renal impairment. In a patient with impaired kidney function, reduce ethambutol dose according to the drug serum concentration.

Adverse effects: Dose-dependent optic neuritis leading to impairment of visual acuity and colour vision. Early changes are usually reversible and prompt withdrawal may prevent blindness. Occasionally, signs of peripheral neuritis, especially in the legs, have been reported. May precipitate attacks of gout since ethambutol can increase uric acid concentration.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

THIOACETAZONE/ISONIAZID

Tablet: 50 mg thioacetazone + 100 mg isoniazid, 150 mg thioacetazone + 300 mg isoniazid

Uses: A component of phase 2 of the 8-month antituberculosis regimens currently recommended by WHO.

Dosage: This fixed-dose combination tablet is used in phase 2 of WHO 8-month treatment schedule.

Adults and children: 2.5 mg/kg thioacetazone + 5 mg/kg isoniazid daily.

Contraindications: Avoid in patients with HIV infection. Thioacetazone has been reported to produce a high incidence of serious and sometimes fatal cutaneous hypersensitivity reactions in HIV-infected patients. Do not give thioacetazone to patients with liver impairment or renal failure.

Precautions: The efficacy and toxicity of thioacetazone should be determined within a community before it is used since there appear to be geographical differences.

Withdraw immediately if rash or other signs related to hypersensitivity occur. Thioacetazone may potentiate the ototoxic effect of streptomycin.

Adverse effects: Refer to information given for isoniazid. Thioacetazone frequently causes gastrointestinal disorders (nausea, vomiting, diarrhoea), hypersensitivity reactions (including conjunctivitis), vertigo and skin rashes. The incidence of these adverse events appears to vary from country to country.

Fatal exfoliative dermatitis and acute hepatic toxicity with jaundice can occur. Thioacetazone may cause agranulocytosis, thrombocytopenia and aplastic anaemia. Acute haemolytic anaemia may occur. However, a large percentage of patients will have some minor degree of anaemia.

Drug interactions: These will appear in tabulated form in the appendix of the published edition of the WHO Model Formulary.

ETHAMBUTOL/ISONIAZID

Tablet: 400 mg ethambutol + 150 mg isoniazid

Uses: Ethambutol is an optional component of several combined antituberculosis regimens and isoniazid is a component of all combined antituberculosis regimens currently recommended by WHO. This fixed-dose combination can be substituted for the thioacetazone + isoniazid combination in patients, who have adverse effects due to thioacetazone.

Dosage: 25 mg/kg ethambutol + 5 mg/kg isoniazid. This fixed-dose combination tablet can be used for

the WHO 8-month regimen (see table on page 258) and is always given daily. The combination tablets are not suitable for children.

Contraindications, precautions, adverse effects and drug interactions: Refer to information given for each substance.

RIFAMPICIN/ISONIAZID/ PYRAZINAMIDE

Tablet: 150 mg rifampicin + 75 mg isoniazid + 400 mg pyrazinamide, 150 mg rifampicin + 150 mg isoniazid + 500 mg pyrazinamide

Uses: All three drugs are components of phase 1 of the 6- and 8-month antituberculosis regimens recommended by WHO.

Dosage: The combination tablets are not suitable for children.

For daily use

Adults: 10 mg/kg rifampicin + 5 mg/kg isoniazid + 25 mg/kg pyrazinamide.

For three times weekly use

Adults: 10 mg/kg rifampicin + 10 mg/kg isoniazid + 35 mg/kg pyrazinamide at each administration.

Contraindications, precautions, adverse effects and drug interactions: Refer to information given for each substance.

BCG VACCINE (DRIED)

Intradermal injection

Uses: To confer active immunity against tuberculosis.

Dosage: Inject the vaccine intradermally. Be careful not to inject vaccine subcutaneously.

Neonates and infants: 0.05 ml by intradermal injection in the arm over the insertion of the deltoid muscle.

Children over 1 year of age: 0.1 ml by intradermal injection in the arm over the insertion of the deltoid muscle.

Contraindications: Generalized oedema; hypogammaglobulinaemia and immunodeficiency resulting from treatment with antimetabolites, irradiation or systemic corticosteroids.

Precautions: Do not inject into skin sites with infective dermatosis, such as scabies.

Adverse effects: Lymphadenitis, osteitis and localized necrotic ulceration may occur. Very rarely, cases of disseminated BCG infection have been reported in immunodeficient patients.

TUBERCULIN (PURIFIED PROTEIN DERIVATIVE)

Intradermal injection

Uses: A diagnostic agent for detecting cell-mediated skin-reactivity to tuberculin.

Dosage and administration: Mantoux test: A special tuberculin syringe is used to inject 0.1 ml of tuberculin (5 IU) intradermally into the flexor surface of the upper forearm after cleansing with acetone or ether. The needle is held parallel to the skin and downward pressure applied until the point penetrates the superficial layers of the skin. It is then moved forward to the intended site of injection where a weal of 7 mm in diameter is raised. The test, which is read after 48–72 hours, is regarded as positive if an area of more than 10 mm diameter around the injection site is indurated.

Precautions: Avoid contact with open cuts, abraded or diseased skin, the eyes or mouth.

WHO MODEL PRESCRIBING INFORMATION

Drugs Used in Skin Diseases

WHO Model Prescribing Information provides up-to-date and independent clinical information on essential drugs, including details of dosage, uses, contraindications, precautions and adverse effects. It is intended as source material for adaptation by national authorities, in particular in developing countries.

This volume includes drugs used for treating parasitic, fungal, bacterial and viral infections of the skin, bites and stings, pigmentary disorders, malignant melanoma, dermatoses and other commonly encountered skin diseases.

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