

Essential Drugs

Tuberculosis: a persistent but treatable disease

Tuberculosis occurs worldwide and remains an important cause of morbidity and mortality in many developing countries. Each year, it is estimated to affect about 10 million people and to cause 3 million deaths worldwide. Whereas its prevalence has declined considerably in the industrialized world within the last fifty years, it has re-emerged among patients with HIV infection.

The disease develops in only a small proportion of individuals infected with the causative mycobacteria, *M. tuberculosis*, *M. bovis* and, in a few instances, *M. africanum*. Most cases are caused by *M. tuberculosis*, which is pathogenic only in man. It is generally transmitted in airborne droplets dispersed by patients with infectious pulmonary disease, and children are at particularly high risk if there is a family contact. *M. bovis* is additionally transmitted in the milk of diseased cows.

Primary infection occurs when phagocytic defences fail locally and bacilli proliferate in macrophages, usually in a discrete alveolar focus. This may give rise to mild fever and malaise, particularly when the regional lymph-nodes are involved, but most cases are asymptomatic. When the immune system is competent the infection is contained within 3 to 6 weeks. All that then remains is a solitary granuloma, typically in the lungs or the regional lymph-nodes, but sometimes — as a result of dispersion of infected macrophages — in a more distant focus.

Occasionally, the entire immune system is overwhelmed, particularly in infants and individuals who are immunodeficient, malnourished or debilitated. Massive haematogenous spread of the infection results either in acute miliary tuberculosis, or in tuberculous meningitis. Diagnosis of these conditions, which is rarely possible on clinical examination alone, is confirmed by characteristic chest X-ray changes and by demonstrating the presence of acid-fast bacilli in the cerebrospinal fluid.

A healed primary infection normally confers substantial immunity. However, dormant lesions may be

reactivated by malnutrition, corticosteroid therapy or immunosuppressive drugs and diseases, including HIV infection. Constitutional symptoms are prominent in these cases of post-primary tuberculosis which may also result from exogenous reinfection where the disease is highly prevalent. Malaise, loss of weight, low-grade fever and night sweats supervene as the disease progresses. In most cases, the major focus of infection is in the lungs, but it may be elsewhere if haematogenous or lymphatic spread occurs. Lymph nodes, kidneys, bones, the genital tract, the brain and the meninges are particularly vulnerable. The typical granulomatous foci tend to caseate, cavitate and fibrose. In the lungs, caseous lesions often liquefy and drain into the bronchial tree giving rise to persistent cough, copious sputum and episodes of haemoptysis of varying degree. Bleeding can be massive when a bronchial artery is eroded, and a risk of miliary tuberculosis arises whenever a caseous focus ruptures into the bloodstream.

Prevention

The incidence of tuberculosis falls wherever living standards are raised and pasteurization of milk is introduced. Where the disease remains highly prevalent, routine immunization of infants shortly after birth with BCG vaccine derived from bacille Calmette-Guérin, (an attenuated strain of *M. bovis*) is a highly cost-effective measure. This has been estimated, in several settings, to reduce the incidence of meningeal and miliary tuberculosis in early childhood by 50 to 100 per cent. However, estimates of its effectiveness in older children and adults have differed greatly from region to region.

Chemoprophylaxis with isoniazid can prevent the development of clinically-apparent disease in close contacts and other persons at high risk. Adults are particularly exposed to a slight risk of hepatitis and healthy individuals are not readily persuaded to take it regularly. In most countries the limited resources available for control programmes are more effectively directed to case-finding and treatment. All members of the immediate family and other close contacts of smear-positive cases should be traced and followed up for at least one year.

Chemotherapy

Effective chemotherapy rapidly reduces the population of viable bacilli and consequently reduces the risk of transmission. Treatment of smear-positive cases should therefore be accorded highest priority in governmental control programmes. Health workers should be trained to recognize the clinical features of pulmonary tuberculosis and to send sputum from suspected cases to a laboratory with facilities for smear examination and, if possible, culture. Chest X-rays can also provide strong presumptive evidence of disease, but radiological screening is usually too costly to be undertaken on a community scale and efforts should always be made to obtain bacteriological confirmation.

Institutional care is essential for those who fail to respond to treatment, those who are severely ill (particularly as a result of a serious complication such as massive haemoptysis or pyopneumothorax) and those who are not ambulant because of tuberculous disease in the hip or spine. Most other patients can be treated satisfactorily at home provided there is assurance that they will take their drugs regularly. Corticosteroids have no place in the routine management of tuberculosis but, in a hospital setting, short courses are of value in treating patients with pleural effusions, tuberculous meningitis and acute miliary tuberculosis associated with dyspnoea. Surgical resection is now necessary only in rare cases of severe post-tuberculous bronchiectasis particularly when this is a cause of repeated haemoptysis.

Five drugs are currently regarded as essential in the management of tuberculosis — isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol. Thioacetazone is also widely used in many developing countries where its low price is considered to offset its relative lack of potency. Other drugs, including para-aminosalicylic acid, kanamycin, cycloserine, capreomycin, viomycin and ethionamide, can be of value in treating patients with multiple drug-resistant disease but, in general, they are more expensive and more toxic.

The treatment of tuberculosis is challenging in several respects:

- tubercle bacilli are vulnerable to bactericidal drugs only when they are metabolically active and replicating;

- small subpopulations of bacilli remain semi-dormant indefinitely and become active transiently — and thus vulnerable to bactericidal agents — only for very short periods of time; and
- drug-resistant mutants can exist even in populations of bacilli never previously exposed to antibiotics.

An ideal antituberculosis drug, apart from being cheap and of low toxicity, would consequently need to possess:

- potent bactericidal activity against metabolically-active bacilli;
- potent sterilizing activity against semi-dormant persisting bacilli; and
- potential to suppress the emergence of resistant organisms throughout the period of chemotherapy.

No known chemotherapeutic agent possesses each of these properties to a degree that renders it self-sufficient. At least two drugs must be administered concomitantly during the first two months of treatment to suppress the emergence of resistance and, in all cases, treatment must be continued for several months longer before there can be reasonable assurance of cure.

Properties of antituberculosis drugs

The therapeutic requirements set out above also provide a convenient means for classifying the available antituberculosis drugs:

Bactericidal agents

Isoniazid, which decimates the bacillary population within a few days of starting treatment is unrivalled in its bactericidal potency. Rifampicin and ethambutol are moderately active, while streptomycin, pyrazinamide and thioacetazone have little or no bactericidal action. The intensity of the bactericidal effect determines the rate at which viable tubercle bacilli disappear from the sputum during the first few days of chemotherapy. It has little influence, however, on the speed at which less vulnerable bacilli are subsequently eliminated.

Sterilizing agents

It is the sterilizing activity of a treatment regimen that determines the duration for which it must be taken.

Rifampicin and pyrazinamide are particularly effective in eliminating subpopulations of bacilli that are unresponsive to other drugs. Rifampicin is active against semi-dormant or intermittently-active bacilli because it has the potential to kill these organisms within the short intervals that they are vulnerable to chemotherapeutic attack. Because it is active in an acidic environment, pyrazinamide is uniquely effective against quiescent bacilli within macrophages and in zones of acute inflammation. It is not of value during the later phases of treatment, after the acute inflammatory response has subsided.

Inhibitors of acquired resistance

Isoniazid and rifampicin are both effective in suppressing the proliferation of drug-resistant mutants since their inhibitory effect is adequately sustained even when occasional doses are taken irregularly. Streptomycin and ethambutol are less efficient in this respect, while pyrazinamide and thioacetazone are the least effective.

Preferred treatment regimens

National chemotherapy policies need to be reviewed periodically since advances continue to be made in the treatment of the disease. When decisions are taken, the higher costs of the more potent drugs should always be set against the savings that accrue from shorter treatment regimens and a lower incidence of therapeutic failure and relapse. Six months sustained treatment is generally adequate to cure the disease if isoniazid and rifampicin are taken throughout. If rifampicin is taken only during the first phase of therapy the period of treatment must be extended by at least two months. Regimens that do not include either rifampicin or pyrazinamide must be sustained for at least 12 months to assure elimination of persistent organisms.

Regimens recommended by WHO on the basis of extensive field trials are detailed on pages 36 and 37. Each regimen has produced cure rates approaching 100 per cent when drug-taking has been fully supervised and one of them should be selected for all newly confirmed cases of tuberculosis. The six-month courses of daily isoniazid and rifampicin, supplemented by pyrazinamide for the first two months, are widely regarded as the most effective and, because these drugs penetrate freely into the cerebrospinal fluid, they should always be available for use in patients with tuberculous meningitis.

Where drug-resistant bacilli are frequently responsible for new infections, and when treating severely-

ill patients with extensive active lesions, ethambutol or streptomycin should be added to the standard regimens for the first two months. Primary resistance to ethambutol is rare and the need to inject streptomycin intramuscularly demands supervision and helps to assure compliance. However, the injections are very painful and disposable needles must be employed, or sterilization assured, to exclude transmission of hepatitis virus and HIV infection. Because it can so readily cause permanent deafness and vestibular damage, streptomycin should never be used during pregnancy. Both the clinical condition of the patient and plasma concentrations of the drug must be monitored throughout treatment.

An eight-month regimen, comprising two months supervised administration of isoniazid, rifampicin, pyrazinamide and either ethambutol or streptomycin, followed by six months self-administered isoniazid and thioacetazone, is still widely used in some countries to reduce drug costs. In practice, this saving can be more than offset by the necessity for more prolonged case management.

The twelve-month regimens are much less effective and should be used only when no other option exists.

Monitoring the therapeutic response

There is evidence that compliance among patients is improving now that shorter treatment regimens are available, but unreliable drug-taking remains the most important cause of therapeutic failure. The need to adhere rigorously to treatment schedules must be emphasized repeatedly to every patient. Whenever possible, drug administration should be supervised in an institutional setting for at least the first two months. Where the facilities for outpatient care are suitably developed, full supervision of treatment can also be arranged by using the intermittent regimens. When professional supervision is not possible, another member of the household or a volunteer in the community should be taught to assume this responsibility. Tablets containing isoniazid and rifampicin, or isoniazid, rifampicin and pyrazinamide in fixed dosage combination are sometimes preferred to single drugs in the expectation that they will promote compliance and reduce the risk of acquired resistance. They should be used, however, only if their bioavailability has been adequately assured. Treatment failures have resulted from poorly-formulated combination products.

Where no other possibility exists, the response to treatment has to be assessed by monitoring the patient's weight, the erythrocyte sedimentation rate and other clinical indices. However, whenever resources permit, the response to treatment should be monitored by routine microbiological examination of cultures as well as smears. Reliance upon smears alone can be misleading since non-culturable and hence non-infective bacilli may persist in the sputum for several months after successful treatment. None the less, smear examination remains a useful indicator of compliance. Paired specimens of sputa should be taken, firstly, after 2 months and, secondly, after 5 months of treatment. If either of the first pair is positive, two further pairs should be examined at monthly intervals and, if bacilli are again detected, the patient should be transferred to another regimen. The same action should be taken if either of the specimens taken at 5 months is positive.

Treatment of relapsing and unresponsive disease

Most cases of chronic or relapsing tuberculosis are the result of irregular, inadequate administration of prescribed drugs or of less potent regimens used in the past. Whenever possible, the drug sensitivity of the bacilli should be established, and previous treatment should always be reviewed to determine whether resistance has occurred and how it is likely to have happened. In the absence of reliable sensitivity tests, treatment with isoniazid, rifampicin and ethambutol should be instituted for 8 months, supplemented with pyrazinamide for the first 2 months and with streptomycin for the first 3 months. All drugs should be administered under strict supervision for at least the first 2 months, preferably in a hospital setting.

Drugs used in pregnancy

Treatment should never be interrupted or postponed during pregnancy or at any other time when immunological resistance to the disease is reduced. However, the fetus should never be exposed to streptomycin because of the risk of auditory and vestibular nerve damage. Since, as a general principle, as few drugs as possible should be administered during pregnancy and for the shortest period of time necessary, the six-month regimen of daily rifampicin and isoniazid supplemented with pyrazinamide holds advantage.

Promising developments

Various newly-developed antimicrobial substances have antimycobacterial activity. The 4-fluoroquinolones are promising bactericidal agents. Other compounds of interest include rifamycin derivatives with long half-lives. These, it is hoped, may provide a basis for fully supervised intermittent regimens. Combinations of clavulanic acid and beta-lactam antibiotics are also being assessed in patients.

Tuberculosis and HIV infection

Because of immunosuppression, patients with HIV infection are at high risk of developing clinical tuberculosis. The disease, which is frequently atypical and extrapulmonary, often antedates manifestations of AIDS by months or even years. Standard 6 or 8-month regimens are usually curative. Whether subsequent chemoprophylaxis should be offered routinely to HIV-infected individuals will eventually be determined by the results of ongoing trials involving, amongst others, regimens based upon isoniazid alone, rifampicin alone and a combination of rifampicin and pyrazinamide.

Although concern has been expressed about disseminated disease resulting from BCG vaccination in HIV-positive individuals, very few cases have been reported and the balance of evidence currently indicates that, in the absence of signs suggestive of AIDS, every infant should be vaccinated, regardless of whether the mother is HIV-positive.

ISONIAZID

*Tablet 100 mg, 300 mg
Injection 25 mg/ml in 2-ml ampoule*

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. It is largely excreted into the urine within 24 hours, mostly as inactive metabolites.

Uses

A component of all antituberculosis chemotherapeutic regimens currently recommended by WHO (see pages 34 and 35).

CHEMOTHERAPY REGIMENS RECOMMENDED BY WHO

| 6-month regimens | <i>Phase 1: 2 months</i> | <i>Phase 2: 4 months</i> |
|--|--|---|
| isoniazid | 5 mg/kg/day | 5 mg/kg/day or 15 mg/kg 3 times weekly |
| rifampicin | 10 mg/kg/day | 10 mg/kg/day or 3 times weekly |
| pyrazinamide | 35 mg/kg/day | |
| <i>supplemented, when primary resistance is demonstrated, either by:</i> | | |
| streptomycin or ethambutol | 15–20 mg/kg/day 25 mg/kg/day | |
| Alternatively | <i>Phase 1: 2 months</i> | <i>Phase 2: 4 months</i> |
| isoniazid | 15 mg/kg 3 times weekly | 15 mg/kg 3 times weekly |
| rifampicin | 10 mg/kg 3 times weekly | 10 mg/kg 3 times weekly |
| pyrazinamide | 50 mg/kg 3 times weekly | |
| <i>together with either:</i> | | |
| streptomycin or ethambutol | 15–20 mg/kg 3 times weekly 25 mg/kg/day | |

| 8-month regimen | <i>Phase 1: 2 months</i> | <i>Phase 2: 6 months</i> |
|----------------------------------|-------------------------------------|--------------------------|
| isoniazid | 5 mg/kg/day | 5 mg/kg/day |
| rifampicin | 10 mg/kg/day | |
| pyrazinamide | 35 mg/kg/day | |
| thioacetazone | 4 mg/kg/day | 4 mg/kg/day |
| <i>together with either:</i> | | |
| streptomycin or ethambutol | 15–20 mg/kg/day 25 mg/kg/day | |

| <i>(Chemotherapy regimens recommended by WHO)</i> | | |
|---|-----------------------------|-----------------------------|
| 12-month regimens | | |
| | <i>Phase 1: 2 months</i> | <i>Phase 2: 10 months</i> |
| isoniazid | 5 mg/kg/day | 5 mg/kg/day |
| streptomycin | 15–20 mg/kg/day | |
| <i>together with either:</i> | | |
| thioacetazone or ethambutol | 4 mg/kg/day 25 mg/kg/day | 4 mg/kg/day 15 mg/kg/day |
| Alternatively | | |
| | <i>Phase 1: 2 months</i> | <i>Phase 2: 10 months</i> |
| isoniazid | 5 mg/kg/day | 15 mg/kg twice weekly |
| streptomycin | 15–20 mg/kg/day | 15–20 mg/kg twice weekly |

Isoniazid is also occasionally used alone in a prophylactic sense in order to prevent:

- transmission to family contacts at high risk of disease, and
- recrudescence of infection in immunodeficient individuals.

Dosage and administration

Isoniazid is normally taken orally. However, it may be administered to critically ill patients intramuscularly.

Treatment (combination therapy):

Adults and children: 5 mg/kg/day or 15 mg/kg 2 or 3 times weekly.

Prophylaxis

Adults and children: 10 mg/kg/day (maximum 300 mg daily) for 6 months to 1 year.

Contraindications

- Known hypersensitivity to isoniazid.
- Active hepatic disease.

Precautions

Serum concentrations of hepatic transaminases should be monitored whenever possible.

Patients at risk of peripheral neuropathy as a result of malnutrition, alcoholism or diabetes should additionally receive pyridoxine, 10 mg daily. Where the standard of health in the community is low this should be offered routinely.

Epilepsy should be effectively controlled since isoniazid may provoke attacks.

Use in pregnancy

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

Adverse effects

Isoniazid is generally well-tolerated at recommended doses.

Systemic or cutaneous hypersensitivity reactions occasionally occur during the first weeks of treatment. They can usually be suppressed by desensitization in the same way as the more common reactions to streptomycin (see page 38).

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

Hepatitis is an uncommon but potentially serious condition that can usually be averted by prompt withdrawal of treatment. A sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is usually not of serious significance. If it regresses rapidly when dosage is suspended, it is unlikely to recur when treatment is reinstated.

Drug interactions

Isoniazid tends to raise plasma concentrations of phenytoin and carbamazepine by inhibiting their metabolism in the liver.

Absorption is impaired by aluminium hydroxide.

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 can be of value if instituted within a few hours of ingestion. Subsequently, haemodialysis may be of use. Administration of pyridoxine may prevent peripheral neuritis.

Storage

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

RIFAMPICIN

Capsule or tablet 150 mg, 300 mg

A semisynthetic derivative of rifamycin B, a complex macrocyclic antibiotic which inhibits nucleic 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 extra-cellular locations.

Rifampicin is lipid soluble. Following oral administration, it is rapidly absorbed and distributed throughout

the cellular tissues and all body fluids including the cerebrospinal fluid. A single dose of 600 mg produces a peak serum concentration of about 10 micrograms/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.

Uses

A component of all six and eight-month anti-tuberculosis chemotherapeutic regimens currently recommended by WHO (see pages 34 and 35).

Dosage and administration

Rifampicin should preferably be taken at least 30 minutes before meals, since food impairs its absorption.

Adults and children: 10 mg/kg (maximum 600 mg)/day or 2 or 3 times weekly.

Contraindications

- Hypersensitivity to rifamycins.
- Hepatic dysfunction.

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 event it should be immediately and definitively withdrawn. Patients should be warned that treatment may produce reddish coloration of urine, tears, saliva and sputa.

Use in pregnancy and lactation

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

Vitamin K should be administered routinely at birth because of a risk of post-natal haemorrhage in the neonate.

Breast-feeding should be avoided since rifampicin is excreted in milk.

Adverse effects

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur during intermittent (once or twice-

weekly) administration. Temporary oliguria, dyspnoea and haemolytic anaemia have also been reported. These reactions subside when daily dosage is instituted.

Moderate rises in serum 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 dose of 10 mg/kg.

Drug interactions

Rifampicin induces hepatic enzymes, and may increase the dosage requirements of drugs metabolized in the liver. These include corticosteroids, steroidal contraceptives, oral hypoglycaemic agents, oral anticoagulants, dapsone, phenytoin and digitalis glycosides. Patients should consequently be advised to use a non-hormonal method of birth control throughout treatment and for at least 1 month subsequently.

Biliary excretion of radiocontrast media and sulphobromophthalein 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 may depress function of the central nervous system. There is no specific antidote and treatment is supportive.

Storage

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

RIFAMPICIN & ISONIAZID

Tablet 150 mg + 100 mg, 300 mg + 150 mg

A fixed combination of rifampicin and isoniazid which has been developed as an aid to compliance. It is essential that all such products are shown to have adequate bioavailability.

Uses

A component of all six-month antituberculosis chemotherapeutic regimens currently recommended by WHO (see pages 34 and 35).

Dosage and administration

Adults: 4 tablets once daily.

Children: not suitable for paediatric use.

For contraindications, precautions, use in pregnancy, adverse effects and drug interactions, refer to sections on the separate components.

Storage

Capsules should be stored in tightly closed containers.

PYRAZINAMIDE

Tablets 500 mg

Pyrazinamide, a synthetic analogue of nicotinamide, is weakly bactericidal against *M. tuberculosis*, particularly in the relatively acidic intracellular environment of macrophages and in areas of acute inflammation. It is effective during the first 2 months of treatment while acute inflammatory changes persist and 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 is excreted largely in the urine.

Uses

A component of all six and eight-month antituberculosis chemotherapeutic regimens currently recommended by WHO (see pages 36 and 37).

Dosage (for the first two months)

Adults and children 35 mg/kg/day or 50 mg/kg 2 or 3 times weekly.

Contraindications

- Known hypersensitivity to pyrazinamide.
- Severe hepatic impairment.
- Gout.

Precautions

Patients with diabetes should be carefully monitored since blood glucose concentrations may become labile.

Use in pregnancy

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

Adverse effects

Pyrazinamide is usually well tolerated. 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, but these frequently revert to normal even if treatment is not interrupted. Severe hepatotoxicity is rare.

A degree of hyperuricaemia always occurs as a result of inhibition of renal tubular secretion, but this is usually asymptomatic. Gout requiring treatment with allopurinol occasionally develops. Arthralgia, particularly of the shoulders, commonly occurs and is responsive to simple analgesics. Both hyperuricaemia and art-ralgia may be reduced by intermittent administration.

Overdosage

Little has been recorded on the management of pyrazinamide overdose. Acute liver damage and hyperuricaemia have been reported. Treatment is essentially symptomatic. 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.

STREPTOMYCIN

powder for injection 1 g base (as sulfate) in vial

An aminoglycoside antibiotic derived from *Streptomyces griseus* which is used in the treatment of tuberculosis and sensitive Gram-negative infections. It is not absorbed from the gastrointestinal tract but, after intramuscular administration, it diffuses readily into the extracellular component of most body tissues and it attains bactericidal concentrations, particularly in tuberculous cavities. Little normally enters into the cerebrospinal fluid, although penetration increases when the meninges are inflamed. The plasma half-life, which is normally 2–3 hours, is considerably extended in the newborn, in the elderly and in patients with severe renal impairment. It is excreted unchanged in the urine.

Uses

A component of several combined antituberculosis chemotherapeutic regimens currently recommended by WHO (see pages 34 and 35).

Dosage and administration

Streptomycin must be administered by deep intramuscular injection. Disposable needles should be used, or adequate sterilization assured, to exclude any risk of transmitting viral pathogens.

Adults: 15–20 mg/kg/day or 2 or 3 times weekly. Patients over 60 years may not be able to tolerate more than 750 mg daily.
Children: 15–20 mg/kg either daily or twice weekly.

Contraindications

- Known hypersensitivity to streptomycin.
- Auditory nerve impairment.
- Myasthenia gravis.

Precautions

Should hypersensitivity reactions occur, as is common during the first weeks of treatment, streptomycin should be withdrawn immediately. Once fever and skin rash have resolved, desensitization may be attempted starting with doses determined by the severity of the reaction. These range from half the standard dose in mild cases to one-tenth of the dose in severe cases.

Streptomycin should be avoided, whenever possible, in children because the injections are painful, and irreversible auditory and vestibular nerve damage is common. Both the elderly, and patients with renal impairment are also vulnerable to dose-related toxicity resulting from accumulation. Serum levels should be monitored periodically and dosage adjusted appropriately to ensure that "trough" plasma concentrations, determined when the next dose is due, do not rise above 4 micrograms/ml.

Use in pregnancy

Streptomycin should not be used in pregnancy. It crosses the placenta and is liable to cause auditory nerve impairment and nephrotoxicity in the fetus.

Adverse effects

Injections are painful and sterile abscesses can form at injection sites.

Permanent impairment of hearing and vestibular function, which may progress even after withdrawal

of treatment, is the commonest serious dose-related adverse effect of streptomycin. Headache, vomiting, vertigo and tinnitus are early clinical indications of dysfunction.

Streptomycin is less nephrotoxic than other aminoglycoside antibiotics. None the less, close monitoring of renal function is necessary. Dosage must be immediately reduced by half if urinary output falls, if albuminuria occurs or if tubular casts are detected in the urine.

Haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia and lupoid reactions are rare adverse effects.

Protective gloves should be worn when streptomycin injections are administered to avoid sensitization dermatitis.

Drug interactions

Other ototoxic or nephrotoxic drugs should not be administered to patients receiving streptomycin. These include other aminoglycoside antibiotics, amphotericin B, cephalosporins, cisplatin, cyclosporin, etacrynic acid, furosemide, mannitol, urea and vancomycin.

Streptomycin may also potentiate the effect of neuromuscular blocking agents administered during anaesthesia.

Overdosage

Haemodialysis can be beneficial. There is no specific antidote and treatment is supportive.

Storage

Solutions retain their potency for 48 hours after reconstitution at room temperature and for up to 14 days when refrigerated. Powder for injection should be stored in tightly closed containers protected from the light.

ETHAMBUTOL

tablets 100 mg, 400 mg (hydrochloride)

Ethambutol, a synthetic congener of ethylene diamine, is bactericidal against *M. tuberculosis*, *M. bovis* and other atypical mycobacteria. It is used in combination with other antituberculosis drugs to prevent or delay the emergence of resistant strains. It is readily absorbed from the gastrointestinal tract. Peak plasma concentrations, which are attained in 2–4 hours, decay with a half-life of 3–4 hours. It is

excreted in the urine both unchanged and as inactive hepatic metabolites.

Uses

An optional component of several combined antituberculosis chemotherapeutic regimens currently recommended by WHO (see pages 34 and 35) particularly when primary resistance to other drugs is suspected.

Dosage

Adults and children: 25 mg/kg/day for no more than 2 months followed by 15 mg/kg/day or 30 mg/kg 3 times a week.

Dosage must always be carefully calculated on a weight basis in order to avoid toxicity.

Contraindications

- Known hypersensitivity to ethambutol.
- Pre-existing optic neuritis from any cause.
- Children too young to report symptomatic visual disturbances.
- Patients with a creatinine clearance of less than 50 ml/minute.

Precautions

Patients should be advised to discontinue treatment immediately and to report to a doctor should their sight or perception of colour deteriorate. Patients who are too young or who are otherwise unable to comprehend this warning should not receive ethambutol.

Whenever possible, renal function should be assessed prior to treatment.

Use in pregnancy

Where there is no evidence of primary resistance, the six-month regimen based upon isoniazid, rifampicin and pyrazinamide should be used. However, ethambutol may be used subject to the above precautions.

Adverse effects

Dose-dependent optic neuritis can readily result in impairment of visual acuity and colour vision. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Signs of peripheral neuritis occasionally develop in the legs.

Overdosage

Emesis and gastric lavage should be undertaken within a few hours of ingestion. Subsequently,

dialysis may be of value. There is no specific antidote and treatment is supportive.

Storage

Tablets should be stored in well-closed containers.

THIOACETAZONE + ISONIAZID

tablet 50 mg + 100 mg, 150 mg + 300 mg

Thioacetazone, a thiosemicarbazone which is bacteriostatic, is used in antituberculosis chemotherapy only to inhibit the emergence of resistance to isoniazid, particularly in regimens that do not include rifampicin. It is available in fixed combinations which are almost as cheap as isoniazid alone and which are intended to promote compliance.

It is well absorbed from the gastrointestinal tract. Peak plasma concentrations are attained after 4–6 hours and the plasma half-life is approximately 12 hours. About one-third of the oral dose is excreted in the urine unchanged.

Uses

A component of some of the longer antituberculosis chemotherapeutic regimens currently recommended by WHO (see pages 34 and 35).

Dosage

Adults: 150 mg thioacetazone + 300 mg isoniazid daily.

Children: 50 mg thioacetazone + 100 mg isoniazid daily.

Contraindications

Known hypersensitivity to either component.

Precautions

Treatment should be withdrawn immediately if a rash or other signs suggestive of hypersensitivity occur.

Use in pregnancy

Where there is no evidence of primary resistance, the six-month regimen based upon isoniazid, rifampicin and pyrazinamide should be preferred.

Adverse effects

Effects attributable to isoniazid are listed on page 35. The thioacetazone component frequently causes nausea, vomiting, diarrhoea and skin rashes. Fatal cases of exfoliative dermatitis and acute hepatic failure have rarely been reported. Cases of agranulocytosis, thrombocytopenia and aplastic anaemia are also on record.

Dose-related ototoxicity is rare, but particularly careful monitoring is required when thioacetazone is used in combination with streptomycin.

Overdosage

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 kept in well-closed containers.

BCG VACCINE (*dried*)

injection

Bacille Calmette-Guérin (BCG) vaccine is a lyophilized preparation of live, attenuated *Mycobacterium bovis*. Various strains, all derived from the same original culture, are used for the manufacture of BCG vaccines. When administered shortly after birth they provide substantial protection against severe forms of tuberculosis of childhood, miliary tuberculosis and tuberculous meningitis. The response has been less consistent when they have been administered to older children and adults.

Uses

To confer active immunity against severe forms of tuberculosis in children.

Unless they have clinical signs suggestive of AIDS, infants under one year born to HIV-infected mothers should be vaccinated

Dosage and administration

It is important that the vaccine be administered intradermally (not subcutaneously) to avoid risk of abscess formation.

The preparation, as distributed, must be reconstituted with an appropriate diluent immediately before injection.

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

Children over one year and adults: 0.1 ml administered as above.

Contraindications

Generalized eczema and infective dermatoses such as scabies or chickenpox. Hypogammaglobulinaemia and immunodeficiency resulting from treatment

with antimetabolites, irradiation or systemic corticosteroids.

Adverse effects

Lymphadenitis, osteitis and localized necrotic ulceration may occur.

Very rarely, cases of disseminated BCG infection have been reported in immunodeficient patients.

This condition is generally readily responsive to antituberculosis chemotherapy.

Storage

Lyophilized vaccines should be protected from light and the storage temperature should not be allowed to rise above 8 °C. BCG vaccine withstands prolonged freezing without deterioration. Unused portions of the reconstituted vaccine should be discarded at the end of the working day.

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