

Essential Drugs

ATYPICAL MYCOBACTERIA

Nontuberculous mycobacteria are ubiquitous in the environment. They exist in food, soil, water, on the surface of many plants, and in buildings, particularly within water pipes. For many years they were thought to be implicated in human disease only as saprophytic contaminants in tuberculous lesions. Now, several species are recognized to be facultative parasites capable of causing chronic granulomatous diseases that can be pathologically indistinguishable from tuberculosis.

These infections are not readily identified because the causative bacteria can be distinguished from *M. tuberculosis* only in specialized reference laboratories. However, they have latterly attracted attention for two reasons. Firstly, wherever tuberculosis has declined within the population at large they now account for a greater proportion of cases of granulomatous disease. Secondly, like tuberculosis, they have emerged as common secondary infections among patients with acquired immunodeficiency syndrome (AIDS).

Most localized infections result from inoculation of organisms into the skin. Pulmonary infection usually occurs only in patients with predisposing disease, while disseminated infection is confined almost exclusively to patients with impaired immune responses. Thus far, there is no evidence of case-to-case transmission.

Clinically, four types of disease are described.

Localized cutaneous lesions

Inoculation of organisms into superficial abrasions and into puncture wounds can result in the formation of localized nodular or ulcerative lesions. The organisms most commonly implicated are *M. marinum*, which colonizes swimming pools and fish aquaria, and *M. ulcerans* which is largely restricted to Australia and some tropical regions and causes deep necrotic lesions known as Buruli ulcers. *M. haemophilum* has more recently been associated with similar lesions in immunosuppressed patients. Abscesses resulting from contaminated injections have most frequently been attributed to two rapidly

growing species, *M. chelonae* and *M. fortuitum*. More such cases are to be anticipated among drug addicts who are immunosuppressed as a result of AIDS but, as yet, most have occurred either among diabetics or as a result of injecting contaminated drugs and vaccines.

Pulmonary disease

The lung is the most frequent site of opportunistic mycobacterial infection and lesions are clinically and radiologically indistinguishable from pulmonary tuberculosis. Predisposing conditions include chronic bronchitis, occupational dust diseases, residual tuberculous lesions, cystic fibrosis, carcinoma, AIDS and other conditions resulting in immunosuppression. Most recorded cases have been attributed to *M. avium-intracellulare*, *M. kansasii* and, to a lesser extent, *M. xenopi* but in some regions *M. scrofulaceum*, *M. chelonae*, *M. szulgai* and *M. malmoense* are also of significance.

Lymphadenitis

The lesions are usually unilateral and self-limiting and most cases occur in children under five. However, lymphadenitis is also sometimes a prominent feature of disseminated disease in adults. Most reported cases have been attributed to the closely-related species *M. avium-intracellulare* and *M. scrofulaceum* (known as the MAIS complex). Any of the organisms implicated in pulmonary disease can also cause lymphadenitis and the other forms of non-pulmonary disease which are more commonly associated with *M. tuberculosis*.

Disseminated disease

Single or multiple foci of granulomatous disease can occur in virtually any system or organ and, when cellular immunity is depressed, dissemination of the infection can occur as rapidly as in miliary tuberculosis. The majority of such cases have been attributed to *M. avium-intracellulare* and to *M. chelonae*.

Management

Diagnosis is dependent upon the clinical characteristics of the disease and identification of the causative organism, when this is possible. Whereas all mycobacterial infections are presumed to give rise

to a positive tuberculin test, conversion usually results from previous infection with *M. tuberculosis* and is thus of little practical help in the diagnosis of nontuberculous infections.

It is not known to what extent the BCG group of vaccines protect against infection by any of the nontuberculous mycobacteria and as yet, no specific vaccines have been developed. The management of established infection is determined by the anatomical focus of the disease, the identity of the organism, the age of the patient, and the competence of the immune system.

General principles

Deep and widely disseminated infections can only be treated by chemotherapy. However, even when treatment is prolonged, the response is uncertain, and surgical resection — now rarely employed in tuberculosis — remains of value in localized nontuberculous pulmonary disease. Surgical excision is also frequently used to hasten resolution of localized lymphadenopathy and of solitary skin lesions, even though these lesions are likely to be self-limiting.

The isolation of nontuberculous mycobacteria from biopsy of a chronic granulomatous lesion generally provides evidence of a causal association. However, the identification of these ubiquitous facultative parasites in sputum or urine requires guarded interpretation. Only when tuberculosis has been rigorously excluded and positive cultures consistently obtained over a period of several weeks should the patient be committed to the prolonged, costly and sometimes hazardous courses of chemotherapy required. Whenever possible, the identity of the causative organism and its sensitivity to candidate antibiotics should be established within a specialized reference laboratory. None the less, *in vitro* sensitivity tests can be misleading and treatment may need to be determined empirically on the basis of published case reports and retrospective surveys.

Selection of chemotherapeutic agents

Most experience has been gained in the treatment of localized pulmonary disease caused by the more prevalent, relatively slow-growing mycobacteria *M. kansasii*, *M. xenopi*, *M. malmoense* and *M. avium-intracellulare* in immunocompetent hosts. Ultimately, they are usually responsive to standard

antituberculosis chemotherapy — even though *M. avium-intracellulare* can be relatively resistant *in vitro*. However, it is often necessary to administer a combination of rifampicin, ethambutol and isoniazid for at least 18 to 24 months.

Several other antibiotics that are not normally used to treat tuberculosis have been claimed to be of value. These include erythromycin in infections due to *M. kansasii*, *M. scrofulaceum* and *M. avium-intracellulare*, and the combination of sulfamethoxazole and trimethoprim in infections attributed to *M. avium-intracellulare*, *M. chelonae*, *M. marinum* and *M. xenopi*. Reports also exist of *M. chelonae* and *M. fortuitum* infections responding to a combination of amikacin and doxycycline, and of *M. marinum* infections responding to minocycline. However, the evidence supporting the use of these drugs is largely anecdotal, and firm recommendations cannot be made.

Clofazimine, which is concentrated in epithelial tissues, the bone marrow and the reticulo-endothelial system, is claimed to be of particular value in the suppression of disseminated disease due to *M. avium-intracellulare*. It has also been advocated in combination with rifampicin in the management of opportunistic infections in patients with AIDS, but insufficient information is currently available to determine whether this regimen has significant effect on morbidity and survival time.

RIFAMPICIN

capsule or tablet 150 mg, 300 mg

A semisynthetic derivative of rifamycin, a complex macrocyclic antibiotic which inhibits nucleic acid synthesis in a broad range of microbial pathogens. 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

In combination with ethambutol and isoniazid in the treatment of infections due to *M. kansasii*, *M. mal-*

moense, *M. xenopi* and *M. avium-intracellulare* in immunocompetent hosts.

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) daily or 2 or 3 times weekly for 24 months. There is some evidence to suggest that *M. kansasii* infections require treatment for only 12 months.

Contraindications

- Hypersensitivity to rifampicin and its derivatives.
- Hepatic dysfunction.

Precautions

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

Patients should be warned that treatment may produce reddish discoloration of urine, tears, saliva and sputum.

Use in pregnancy and lactation

Treatment should not be interrupted or postponed should pregnancy intervene. Vitamin K should be administered routinely at birth because of a risk of perinatal haemorrhage in the neonate.

Adverse effects

Rifampicin is well tolerated by most patients at currently recommended doses, although gastrointestinal intolerance can be unacceptably severe, in which case treatment should be discontinued. Other adverse effects (skin rashes, fever, influenza-like syndrome and thrombocytopenia) are more likely to occur during intermittent (once or twice-weekly) administration, and 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. Women of child-bearing age 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 sulfo-bromophthalein sodium may be reduced and microbiological assays for folic acid and vitamin B₁₂ (cyanocobalamin) disturbed.

Overdosage

Gastric lavage may be of value if undertaken within a few hours of ingestion. Very large doses 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.

ETHAMBUTOL

tablets 100 mg, 400 mg (hydrochloride)

Ethambutol, a synthetic congener of ethylene diamine, is bactericidal against some atypical mycobacteria. 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

In combination with rifampicin and isoniazid in the treatment of infections due to *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. avium-intracellulare* in immunocompetent hosts.

Dosage

Adults and children

25 mg/kg daily for no more than 2 months followed by 15 mg/kg daily or 30 mg/kg 3 times a week for 24 months. There is some evidence to suggest that

M. kansasii infections require treatment for only 12 months.

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

Contraindications

- Known hypersensitivity.
- 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 otherwise unable to comprehend this warning should not receive ethambutol. Whenever possible, renal function should be assessed prior to treatment.

Use in pregnancy

Treatment should not be interrupted or postponed should pregnancy occur.

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 may be of value if 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.

ISONIAZID

tablet 100 mg, 300 mg

injection 25 mg/ml in 2-ml ampoule

Isoniazid, the hydrazide of isonicotinic acid, is bactericidal against some atypical mycobacteria. 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

In combination with rifampicin and isoniazid in the treatment of infections due to *M. kansasii*, *M. malmoense*, *M. xenopi* and *M. avium-intracellulare* in immunocompetent hosts.

Dosage and administration

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

Adults and children

5 mg/kg daily or 15 mg/kg 2 or 3 times weekly for 24 months. There is some evidence to suggest that *M. kansasii* infections require treatment for only 12 months.

Contraindications

- Known hypersensitivity.
- 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, chronic alcohol dependence 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

Treatment should not be interrupted or postponed if pregnancy occurs.

Adverse effects

Isoniazid is generally well-tolerated at recommended doses.

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

Peripheral neuropathy can be averted 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. More often, however, a sharp rise in serum concentrations of hepatic transaminases at the outset of treatment is 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 protected from light.