
WHO Model Prescribing Information

Drugs used in Parasitic Diseases

Second edition



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Preface

WHO's revised drug strategy, as adopted in resolution WHA39.27 of the Thirty-ninth World Health Assembly in 1986, calls for the preparation of model prescribing information which is being developed to complement WHO's Model List of Essential Drugs.¹ The objective is to provide up-to-date source material for adaptation by national authorities, particularly in developing countries, that wish to develop national drug formularies, drug compendia and similar material.²

The information is to be regarded as illustrative rather than normative. It is appreciated that it is not possible to develop an information sheet on a specific drug that is appropriate to circumstances prevailing in each of WHO's Member States and that some countries have already formally adopted texts of their own that have a statutory connotation.

This second edition of the volume on drugs used in parasitic diseases, which was first published in 1990, has been prepared in collaboration with internationally accredited experts and with members of WHO's Expert Advisory Panel on Drug Evaluation and the various WHO expert advisory panels on parasitic diseases. It has also been reviewed by certain non-governmental organizations in official relations with WHO, including the International Federation of Pharmaceutical Manufacturers Associations, the International Pharmaceutical Federation, the International Union of Pharmacology and the World Federation of Proprietary Medicine Manufacturers. The sections on malaria, African trypanosomiasis, cestode infections, schistosomiasis and onchocerciasis have been extensively revised in the light of new developments in the treatment of these diseases.

¹ *The use of essential drugs. Sixth report of the WHO Expert Committee.* Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850).

² For details of volumes already published, see inside back cover.

Drug dosage

Most drug doses are given per kilogram of body weight or as fixed doses calculated for adults of 60 kg.

Storage conditions

Readers are referred to *The International Pharmacopoeia*, 3rd edition, vol. 4 (Geneva, World Health Organization, 1994) for definitions concerning containers for drugs.

Abbreviations used

i.m. intramuscular(ly)
i.v. intravenous(ly)

Protozoa

Amoebiasis and giardiasis

Amoebiasis

Entamoeba histolytica is a protozoan parasite which is usually transmitted from person to person through faecal contamination of food or hands, but may also be transmitted by sexual contact in homosexual men. Ingested cysts release trophozoites that lodge in the caecum and ascending colon where they multiply and form more cysts which are excreted in the faeces. Only certain varieties are pathogenic, and asymptomatic carriers are common in endemic areas. Diagnosis presents difficulties, particularly in epidemiological surveys, because the microscopical techniques used require highly skilled personnel seldom available where infection is most prevalent. Globally, as many as 500 million people may harbour these parasites and several tens of thousands die each year as a consequence of fulminating colitis or liver abscess.

Amoebic dysentery occurs when the parasites invade the intestinal wall and abscesses may develop in the liver or, less frequently, in the lung or brain as a result of haematogenous spread. Skin lesions may also occur. Pregnant women and individuals who are malnourished or immunocompromised are most vulnerable to systemic infection.

Sporadic cases of invasive amoebiasis occur worldwide, but the disease is most prevalent throughout south-east Asia including the Indian subcontinent, south-east and west Africa, and Central and South America.

Prevention

Where there is a high risk of reinfection neither chemoprophylaxis nor mass chemotherapy offers an effective means of control. Prevention is dependent upon eliminating faecal contamination of food, hands and water supplies by:

- instructing primary health care workers on how the disease is transmitted and recognized;
- training communities in personal and family hygiene; and

- efficient sewage disposal and provision of an adequate and safe supply of water.

Treatment

The available drugs are classified broadly as luminal amoebicides, active primarily against organisms in the colonic contents, and systemic amoebicides, active against organisms responsible for invasive disease.

Symptomless carriers

In non-endemic areas, carriers should be treated with a luminal amoebicide which reduces the risk of transmission and protects the patient from invasive amoebiasis. Diloxanide furoate is most widely used, but other compounds, including cefamide, etofamide and teclozan, are also effective.

When the risk of reinfection is high, treatment is not warranted except for mothers responsible for preparing food within a family or for individuals who, as a result of their occupation or lifestyles, are particularly likely to infect others.

Invasive amoebiasis

All patients with invasive disease require treatment, firstly with a systemically active compound and, subsequently, with a luminal amoebicide in order to eliminate any surviving organisms in the colon. Combined preparations have also been used with success. The pathology and clinical expression of amoebiasis vary from region to region and drug regimens are best devised on the basis of local experience.

The availability of metronidazole — and several other 5-nitroimidazoles, including ornidazole, tinidazole and secnidazole — has made the management of most cases simpler and safer (see table on page 8). Parenteral formulations of metronidazole, ornidazole and tinidazole are available for patients too ill to take drugs by mouth. Preliminary studies suggest that the more recently introduced compounds may sometimes act more rapidly, and comparative clinical studies are being conducted. Until their results become widely known the cheapest available preparation should be used. In severe cases of amoebic dysentery, tetracycline lessens the risk of superin-

fection, intestinal perforation and peritonitis when it is given in addition to a systemic amoebicide.

Dehydroemetine, which is too irritant to be taken orally, is claimed by some authorities to remain the most effective tissue amoebicide (but it is closely matched by parenterally administered 5-nitroimidazoles). It is reserved for dangerously ill patients, but these are likely to be most vulnerable to its cardiotoxic effects.

Patients treated with dehydroemetine for hepatic abscess should also receive chloroquine, which has amoebicidal activity and is selectively concentrated in the liver. Needle aspiration is advisable, both when the size of the abscess is likely to compromise effective penetration of the drugs, and when severe hepatic pain and tenderness indicate that rupture is imminent.

Giardiasis

Giardia intestinalis is a flagellated protozoan parasite which frequently coexists with *E. histolytica* and is transmitted in the same way. It occurs worldwide, particularly where sanitation is poor and it is a common cause of both acute and persistent diarrhoea among children in developing countries. Reported prevalence rates range from less than 1% to over 50% and it has been estimated that about 200 million infections occur annually in Africa, Asia and Latin America. Localized epidemics frequently occur in children's institutions. In addition, several large waterborne epidemics have occurred in northern regions of the former USSR, and also in Canada and the USA, where beavers may provide a reservoir of infection.

Ingested cysts release trophozoites that attach firmly to the mucosa of the jejunum. These multiply and eventually form another generation of cysts which are excreted intermittently in the faeces. Many carriers are symptomless, but others lose weight and complain of diarrhoea or gastrointestinal discomfort. Diagnosis requires skilled microscopy, and false-negative tests are common because cysts are excreted in the stools irregularly. Confirmatory examination of jejunal aspirates may be necessary. Extensive infections result in intestinal

malabsorption and impairment of growth. Severe symptoms are more likely to occur in patients who are malnourished, hypochlorhydric or immunocompromised.

Treatment with tinidazole in a single dose or with another 5-nitroimidazole is highly effective and should be offered, when practicable, to all infected patients. Family and institutional contacts should also be treated. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.

Metronidazole

Group: antiprotozoal agent

Tablet 200–500 mg

Injection 500 mg in 100-ml vial

Oral suspension 200 mg (as benzoate)/5 ml

General information

A 5-nitroimidazole derivative with antimicrobial activity against anaerobic bacteria and some protozoa, including *E. histolytica* and *G. intestinalis*.

Metronidazole is almost completely absorbed following oral administration. Its plasma half-life is about 8 hours and it is excreted, largely in the urine, both unchanged and as metabolites.

Clinical information

Uses

Treatment of invasive amoebiasis and giardiasis.

Patients should subsequently receive a luminal amoebicide to eliminate surviving organisms in the colon.

Dosage and administration

Metronidazole should be administered preferably with or immediately after food.

Various dosage regimens are used. The following regimen is widely accepted but definitive recommendations should be based on local experience.

Invasive amoebiasis

Adults and children: 30 mg/kg daily orally in three divided doses after meals for 8–10 days, or i.v. in three divided injections daily until the patient is able to take oral formulations.

The efficacy of shorter oral regimens is

currently being evaluated in controlled trials.

Metronidazole may also be used to treat asymptomatic carriers in non-endemic areas if no luminal amoebicide is available, but it is less effective.

Giardiasis

Adults: 2 g once daily for 3 days.

Children: 15 mg/kg daily in divided doses for 5–10 days.

Comparable doses of tinidazole, ornidazole and secnidazole for both amoebiasis and giardiasis are set out in tabular form on page 8.

Contraindications

- Known hypersensitivity.
- Early pregnancy.
- Chronic alcohol dependence.

Precautions

Treatment should be discontinued promptly if peripheral neuropathy, ataxia or other signs of central nervous dysfunction occur. Such reactions are extremely rare at the recommended doses. None the less, patients with active disease of the central nervous system should be particularly carefully monitored.

The blood count should be frequently checked, particularly in patients with a history of blood dyscrasia and when treatment is extended beyond 10 days.

Patients should be warned not to take alcohol during treatment since disulfiram-like reactions can occur.

Metronidazole (continued)**Use in pregnancy and lactation**

Amoebic dysentery may run a fulminating course during late pregnancy and the puerperium. Treatment with metronidazole may then be life-saving to the mother, but in some cases of severe dysentery surgical resection of the intestine may also be necessary. In less severe infections, metronidazole is best avoided in the first trimester since, in animals, it has been shown to have mutagenic and carcinogenic potential.

It is advisable during treatment to discontinue breast-feeding, particularly of premature infants.

Adverse effects

In general, metronidazole is well tolerated but mild symptoms of headache, gastrointestinal irritation and a persistent metallic taste are common. Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions, which are rare, are most likely to occur during extended courses of treatment. They include stomatitis and candidiasis, reversible leuko-

penia, and sensory peripheral neuropathy, which is usually mild and rapidly reversible.

Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably higher than those currently recommended.

Drug interactions

The action of oral anticoagulants is potentiated. Alcohol may induce abdominal pain, vomiting, flushing and headache.

Phenobarbital and corticosteroids lower plasma levels of metronidazole whereas cimetidine raises them.

Overdosage

No specific treatment exists. Emesis or gastric lavage may be of value within a few hours of ingestion.

Storage

Tablets and suspension should be stored in well-closed containers, protected from light. Metronidazole injection should be kept in single-dose, sealed containers; protected from light.

Typical comparative adult dosage schedules for 5-nitroimidazole derivatives^a

	Amoebic dysentery	Amoebic abscess	Giardiasis
Metronidazole	30 mg/kg daily ^b for 8–10 days	30 mg/kg daily ^b for 8–10 days	2 g daily for 3 days
Tinidazole	2 g daily for 3 days	2 g daily ^b for 5 days	2 g in a single dose
Ornidazole	2 g daily for 10 days	2 g in a single dose ^b	inadequate data available
Secnidazole	2 g in a single dose	1.5 g daily for 5 days	inadequate data available

^a Oral dosage is implied except where otherwise stated.

^b Oral or i.v. dosage.

Diloxanide

Group: luminal amoebicide

Tablet 500 mg of diloxanide furoate

General information

An amoebicide that is active only against organisms in the gastrointestinal contents. Less than 10% of an oral dose is excreted in the faeces, but sufficient amounts reach the colonic lumen to eradicate intraluminal forms of *E. histolytica*. The remainder is hydrolysed within the intestinal mucosa as it is absorbed and subsequently excreted in the urine as the glucuronide. Concentrations attained in tissues, including the intestinal mucosa, are subtherapeutic.

Clinical information

Uses

Amoebiasis:

- treatment of asymptomatic carriers in non-endemic areas
- eradication of residual amoebae in the colonic lumen following treatment of invasive disease with anti-amoebic drugs.

Dosage and administration

Adults: 500 mg three times daily for 10 days.

Children: 20 mg/kg daily in three divided doses for 10 days.

Treatment is regarded as successful if stools remain free of *E. histolytica* for one month. Several specimens should be examined in evaluating the response to treatment.

Contraindications and precautions

Diloxanide appears to be essentially nontoxic and is well suited to outpatient use.

Use in pregnancy

No untoward effects have been demonstrated but treatment is best deferred, when possible, until after the first trimester of pregnancy.

Adverse effects

Mild gastrointestinal symptoms, particularly flatulence, may be troublesome. Pruritus and urticaria can also occur.

Storage

Tablets should be kept in well-closed containers, protected from light.

Dehydroemetine

Group: antiprotozoal agent

Injection 60 mg of dehydroemetine dihydrochloride in 1-ml ampoule

General information

A derivative of emetine which is less toxic than the parent substance. It is claimed by some to be the most effective tissue amoebicide, but it is too

irritant to be taken orally. Following intramuscular injection it is widely distributed in tissues, particularly in the liver and lungs. It is excreted in the urine.

Dehydroemetine (continued)

Clinical information

Uses

Amoebic dysentery:

- as an alternative to parenteral metronidazole or other 5-nitroimidazole derivatives in severely ill patients unable to take drugs orally
- following an inadequate response to 5-nitroimidazoles.

Amoebic abscess:

- dehydroemetine is effective when used alone, but it is usually necessary to give a second course 6 weeks later in patients with extensive hepatic abscesses.

Dosage and administration

Adults: 1 mg/kg daily, to a maximum of 60 mg, for up to 4–6 days. This dosage should be reduced by up to 50% in elderly and severely ill patients.

Children: 1 mg/kg daily for no more than 5 days.

Injections should always be given intramuscularly. Intravenous injection is unacceptably dangerous and holds no advantage. At least 6 weeks should elapse before a second course is administered.

In amoebic dysentery, supplementary treatment with tetracycline reduces the risk of bacterial superinfection.

In hepatic abscess, supplementary treatment with chloroquine, which is selectively concentrated in the liver, may be given orally, either concurrently or immediately afterwards.

All patients should subsequently receive diloxanide by mouth to eliminate surviving organisms in the colon.

Precautions

Dehydroemetine should only be considered as a last resort in patients with pre-existing cardiac, renal or neuromuscular disease.

It should always be administered in a hospital setting.

Heart rate and blood pressure should be carefully monitored and treatment should be stopped immediately if tachycardia, severe hypotension or electrocardiographic changes develop.

Weakness and muscular pain frequently precede more serious toxic effects and serve as a warning to reduce dosage.

Use in pregnancy

Dehydroemetine is toxic to the fetus. However, amoebic dysentery may run a fulminating course in late pregnancy, and in this case treatment with dehydroemetine may be life-saving to the mother.

Adverse effects

Local reactions

The injections are painful. Abscess formation is common. A local eczematous rash may follow inadvertent subcutaneous injection. Generalized urticarial and purpuric rashes are rare.

Neuromuscular effects

Weakness and muscular pain are common, particularly in the limbs and neck. Dyspnoea may also occur as a result of generalized weakness. These symptoms are dose-related and often precede evidence of cardiotoxicity.

Cardiac effects

Hypotension, precordial pain, tachycardia and dysrhythmias are the most frequent signs of cardiac impairment. Electrocardiographic changes, particularly flattening and inversion of the

T wave and prolongation of the Q-T interval, provide an early indication of toxicity.

Drug interactions

Cardiotoxic effects are potentiated

by other drugs liable to cause dysrhythmias.

Storage

Ampoules should not be left exposed to light.

Chloroquine

Group: antiprotozoal agent

Tablet 100mg, 150mg base (as phosphate or sulfate)

[chloroquine base 150mg is equivalent to chloroquine sulfate 200mg or chloroquine phosphate 250mg]

General information

A 4-aminoquinoline used primarily as an antimalarial, but which is also a tissue amoebicide. The 5-nitroimidazoles are more effective in the latter context, but when they are not available it is justifiable to use chloroquine instead. Chloroquine is more frequently used as an adjunct to dehydroemetine in the treatment of hepatic abscess. It is claimed to increase the prospect of cure during the first course of treatment.

Absorption from the gastrointestinal tract is efficient and peak plasma concentrations occur within 2–3 hours. The drug and its metabolites can be detected in the plasma for up to 2 months and in the urine for up to 4 months after a single dose.

Clinical information

Uses

Treatment of amoebic hepatic abscess, as an adjunct to therapy with dehydroemetine.

Dosage and administration

Adults: 600 mg base daily for 2 days,

followed by 300 mg base daily for at least 2–3 weeks.

Children: 10 mg/kg daily for 2–3 weeks; maximum 300 mg base daily.

If a dose is vomited, it must be replaced.

Patients should subsequently receive a luminal amoebicide to eliminate residual organisms in the colonic lumen.

Contraindications

- Known hypersensitivity.

Precautions

Hepatic function should be carefully monitored throughout treatment in patients with pre-existing hepatic disease.

Use in pregnancy

No untoward effects have been demonstrated, but treatment is best deferred, when possible, until after the first trimester of pregnancy.

Adverse effects

In the dosages used for prophylaxis and treatment of parasitic infections, adverse effects are usually mild and reversible.

Chloroquine (continued)

Transient headaches and gastrointestinal symptoms are occasionally troublesome.

Intolerance requiring withdrawal of treatment is rare, although severe pruritus can occur.

Chloroquine may precipitate a severe exacerbation of psoriasis.

Overdosage

Acute chloroquine poisoning is often fatal; the lethal dose may be as low as 50 mg chloroquine base/kg. Nausea, vomiting and drowsiness, which occur rapidly, are followed by slurring of

speech, agitation, visual impairment, breathlessness due to pulmonary oedema, cardiac dysrhythmias, convulsions and coma.

Emesis must be induced, or gastric lavage undertaken, as rapidly as possible if the patient is seen within a few hours of ingestion. Otherwise treatment is symptomatic and is directed particularly to sustaining cardiovascular and respiratory function. Diazepam may help to control convulsions.

Storage

Tablets should be kept in well-closed containers, protected from light and moisture.

Babesiosis, a disease similar to malaria, is an important protozoan infection of wild and domestic animals in western America and Europe. The parasites, *Babesia divergens* (cattle) and *B. microti* (rodents), are transmitted by the bite of ticks, *Ixodes* spp. Infections in humans are rare and most occur in people who are immunocompromised. Transmission by blood transfusion is also on record. The parasite becomes established by invading red blood cells where it multiplies asexually. Other erythrocytes are invaded when infected cells rupture and the cycle is repeated.

Infection with *B. microti* is generally mild, asymptomatic and rapidly self-limiting. *B. divergens* possibly becomes established only in splenectomized patients. It usually produces a fatal infection characterized by hyperpyrexia, haemolytic anaemia and renal insufficiency.

Control

Babesiosis can be prevented by avoiding exposure to ticks in so far as this is practicable, using repellents and screening donated blood.

Treatment

Symptomatic treatment suffices for most patients infected with *B. microti*. A combination of quinine and clindamycin is reported to be successful in the few patients requiring specific treatment, but further confirmation of this claim is required.

There is no evidence that *B. divergens* infections are responsive to chemotherapy.

Free-living amoebae

Members of at least two genera of free-living amoebae, *Naegleria* and *Acanthamoeba*, cause serious disease in humans. Both can cause meningoencephalitis but most infections are attributed to *N. fowleri*, which contaminates the warm stagnant waters of lakes and indoor swimming pools. Disseminated disease can occur if the organism penetrates into the meningeal space through the cribriform plate. This can occur during participation in water sports, particularly water-skiing. *Acanthamoeba* spp occasionally cause sight-threatening corneal keratitis, which is becoming more frequent with the use of contact lenses.

Control

Adequate chlorination of swimming pools, where this is feasible, rapidly kills the amoebae. Wearers of contact lenses should receive precise instructions on lens care and, in particular, they should be warned of the risk of home-made non-sterile saline rinsing solutions.

Treatment

N. fowleri meningoencephalitis is usually fatal. However, a few patients have responded to amphotericin B administered both intravenously and intrathecally. Meningoencephalitis due to *Acanthamoeba* spp is unresponsive to chemotherapy.

Acanthamoeba keratitis usually necessitates corneal grafting although topical antimicrobial therapy may be required for many months before surgery can be undertaken.

Protozoa of the *Leishmania* spp are responsible for several clinically distinctive diseases characterized by chronic inflammatory infiltration, focal necrosis and fibrosis. In some, the lesions are localized to the point of inoculation but, in others, the parasite becomes widely disseminated. Worldwide, some 12 million people are estimated to be infected and over 2 million new cases occur each year.

Some species of the parasite only infect humans. Others also infect dogs, rodents and other mammals. All are transmitted by the same biting vector, the female sandfly. Once inoculated, the parasites are largely contained within local reticuloendothelial cells where they undergo rapid asexual division. However, some of the infected cells re-enter the circulation as macrophages. The intensity of the inflammatory response is an important determinant of the degree to which the disease remains localized and of the clinical sequelae of infection.

Visceral leishmaniasis (kala-azar) is caused by parasites of the *Leishmania donovani* complex, and is endemic in south-west Asia, the Indian subcontinent, China, the Mediterranean area, east Africa and Central and South America. Infected macrophages spread from the site of inoculation to the liver, spleen and bone marrow. The intracellular form of the parasite is conspicuous in large mononuclear cells as ovoid Leishman-Donovan bodies. Clinically, the early phases of the disease are characterized by chronic irregular fever, malaise, anorexia, cough, diarrhoea and secondary infections. Later, progressive enlargement of the spleen, liver and, occasionally, the lymph-nodes is accompanied by anaemia and emaciation. Untreated, it is usually fatal. In some patients — particularly in the Indian subcontinent — chronic granulomatous infiltrations of the skin and patchy hypopigmentation occur one year or more after apparent cure, usually without ulceration.

Cutaneous leishmaniasis comprises two conditions. The Old World variety is caused by *L. tropica*, *L. major*, *L. infantum* and *L. aethiopica*, and is endemic in the Mediterranean area,

western Asia, western areas of the Indian subcontinent and east and west Africa. The New World variety is caused by *L. amazonensis*, *L. mexicana*, *L. peruviana*, *L. guyanensis*, *L. panamensis* and *L. braziliensis* and is endemic in Central and South America (except Chile and Uruguay). Both conditions are characterized by a cell-mediated reaction of varying intensity at the site of inoculation. As immunity develops, healing occurs by fibrosis leaving a prominent scar. The New World variety tends to be more severe and is slower to heal.

Mucocutaneous leishmaniasis is largely confined to South and Central America. It is most frequently caused by *L. braziliensis*, sometimes by *L. panamensis*, and rarely by *L. guyanensis*. A few cases due to *L. aethiopica* have been reported from Ethiopia and Kenya. The primary lesions are those of cutaneous leishmaniasis, often accompanied by regional lymphangitis and lymphadenitis. The disease is characterized by progressive ulceration and erosion of the soft tissues of the mucosa of the nose, mouth and pharynx, known as espundia, which can occur either soon after the initial infection or many years — and even several decades — after apparent resolution of the primary lesions.

Diffuse cutaneous leishmaniasis results from infection with parasites of the *L. mexicana* complex and, sometimes, with *L. aethiopica*. *L. amazonensis* (one of the species of the *L. mexicana* complex) is endemic mainly in Brazil, the Dominican Republic, Mexico and Venezuela, while *L. aethiopica* occurs in Ethiopia and Kenya. The primary lesion extends progressively and the disease is eventually characterized by widespread, irreversible skin thickening and leprosy-like lesions that, once established, do not regress with treatment.

Control¹

Effective control strategies always involve efficient case-finding, parasitological confirmation of the diagnosis and systematic treatment of those infected. These measures may be sufficient to control the diseases that are restricted to humans.

¹ For further information, see *Control of the leishmaniases. Report of a WHO Expert Committee*. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No. 793).

When animal reservoirs exist, additional measures are needed. Aerial spraying of vectors with DDT, malathion, dieldrin or propoxur is too expensive for widespread use. Rodent control can be feasible in open steppe country, but not in remote forested areas. In urban areas, spraying with long-acting insecticides and destruction of stray dogs, which are a reservoir for visceral leishmaniasis, have been effective. Wherever these diseases remain endemic, it is important to minimize contact with sandflies through use of insect repellents and bed-nets and window screens impregnated with pyrethroid insecticides.

As yet, no antileishmanial vaccine has been developed commercially. In some highly endemic areas, however, live cultures of *L. major* (promastigotes) are sometimes deliberately inoculated at an aesthetically acceptable site. Although this is an effective protective measure, the inoculum must be carefully standardized to prevent severe cutaneous lesions from developing, which may remain active for 6 to 9 months if left untreated. Moreover, the recipients become carriers and potential sources of infection to others.

Treatment

Leishmania species differ in their sensitivity to chemotherapeutic agents.

Visceral leishmaniasis is usually responsive initially to the pentavalent antimonial compounds, meglumine antimoniate or sodium stibogluconate. Both dosage and duration of treatment need to be adjusted according to the clinical response. Patients are considered to be clinically cured when no parasites are detected in splenic or bone marrow aspirates. However, biopsies should be carried out again after 3 and 12 months since subsequent relapse is frequent. Antimonials combined with allopurinol, pentamidine and amphotericin B have each been used with success in patients in relapse who have become unresponsive to antimonials alone.

Cutaneous leishmaniasis, including both Old World varieties due to *L. major* and *L. tropica* and New World varieties due to *L. mexicana* and *L. peruviana*, is responsive to intralesional injections of antimonial compounds. Mild lesions can often be

left to heal spontaneously. However, it is preferable to treat *L. tropica* infections with a view to reducing transmission since humans seem to be the only hosts. When the lesion is inflamed or ulcerated, or when obstruction of lymphatic drainage or destruction of cartilage creates a risk of serious disfigurement or disability, antimonials should be administered systemically as well as locally.

L. aethiopica is much less responsive to antimonials at conventional doses and, provided there is no evidence of diffuse cutaneous involvement, the sores can be left to heal spontaneously. *L. guyanensis* infections should always be treated with pentamidine. The initial lesion is small but there is a risk of disseminated disease resulting from lymphatic spread and, occasionally, of mucosal involvement. It is also important to treat all infections due to *L. braziliensis* and the less common *L. panamensis* with antimonials because of the risk of mucosal involvement.

Mucocutaneous leishmaniasis causes permanently disfiguring lesions and *L. braziliensis* infections, in particular, are associated with the added risk of espundia. The latter usually respond to antimonials and, when relapses occur, more extended courses of treatment are often successful. Patients that still fail to respond should receive amphotericin B or pentamidine, although neither treatment is highly satisfactory. Because of their resistance to antimonials, *L. aethiopica* infections should be treated with pentamidine from the outset until complete healing occurs; relapses are rare.

Antigens liberated from dead parasites sometimes induce severe inflammation during the early phases of treatment. Emergency use of corticosteroids may be needed to control pharyngeal or tracheal oedema. Antibiotics may also be needed to treat secondary infections, and plastic surgery offers the only means of ameliorating disfiguring scars.

Diffuse cutaneous leishmaniasis is usually first treated with antimonial compounds, but relapses must be expected. *L. aethiopica* is particularly resistant and repeated courses of pentamidine may be needed until clinical immunity becomes established.

Meglumine antimoniate and sodium stibogluconate

Group: antiprotozoal agent

Injection containing the equivalent of 85 mg/ml (meglumine antimoniate) or 100 mg/ml (sodium stibogluconate) of antimony (Sb^{5+}), in 5-ml ampoule

General information

Pentavalent antimony compounds with leishmanicidal activity, but which are not effective against free flagellated forms *in vitro*. It is uncertain whether they have selective activity against intracellular forms, or whether small amounts are converted intracellularly into a potent trivalent inhibitor of the parasite's glycolytic enzymes.

Since they are poorly absorbed and highly irritant to the gastrointestinal tract they must be administered parenterally or by local injection. Over 80% of the dose is excreted unchanged in the urine within 6 hours.

Clinical information

Uses

Treatment of:

- visceral leishmaniasis
- cutaneous leishmaniasis (except for *L. aethiopica* infections, which are unresponsive)
- diffuse cutaneous leishmaniasis due to *L. amazonensis*
- cutaneous and mucocutaneous leishmaniasis due to *L. braziliensis*.

Dosage and administration

Intramuscular doses are expressed in terms of the equivalent amount of pentavalent antimony (Sb^{5+}). All doses, which are weight-related, are suitable for both adults and children.

Visceral leishmaniasis

Injection of 20 mg Sb^{5+} /kg i.m. daily (to a maximum of 850 mg Sb^{5+}) for a minimum of 20 days. Treatment should be continued until no parasites are detected in consecutive splenic aspirates taken at 14-day intervals.

Patients who relapse following the first course of treatment should be re-treated immediately using the same daily dosage.

Cutaneous leishmaniasis

Except: *L. braziliensis* (see below) and *L. aethiopica* (see pentamidine).

Intralesional injections are effective for early nodular lesions. Infiltration must be thorough and produce complete blanching of the base of the lesion. Systemic therapy is required when lesions are inflamed, ulcerated or situated where scarring can result in disability or disfigurement, and particularly when there is lymphatic obstruction or involvement of cartilage.

Local therapy

Injection of 1–3 ml into the base of the lesion, repeated once, or twice if no response is apparent, at intervals of 1 to 2 days.

Systemic therapy

Injection of 10–20 mg Sb^{5+} /kg i.m. daily until a few days after clinical cure and slit-skin smears are negative. Relapse is unusual.

**Meglumine antimoniate and
sodium stibogluconate (continued)**

**Cutaneous leishmaniasis
(*L. braziliensis*)**

Injection of 20 mg Sb⁵⁺/kg daily i.m. until the lesion is healed and for at least 4 weeks. Relapse is usually associated with inadequate dosage or interrupted treatment. Should relapse occur following a full course of treatment, pentamidine should be used.

**Mucocutaneous leishmaniasis
(*L. braziliensis*)**

Injection of 20 mg Sb⁵⁺/kg daily i.m. until slit-skin smears are negative and for at least 4 weeks. In the event of toxicity or inadequate response, 10–15 mg Sb⁵⁺/kg should be administered every 12 hours for the same period. Patients who relapse should be re-treated for at least twice as long. Those who are unresponsive should receive amphotericin B or pentamidine.

**Diffuse cutaneous leishmaniasis
(*L. amazonensis*)**

Injection of 20 mg Sb⁵⁺/kg daily i.m. for several months after clinical improvement occurs. Relapse must be expected until immunity develops.

Contraindications

- Severe kidney, heart or liver disorders.

Precautions

A protein-rich diet should be provided

throughout treatment and, where possible, iron depletion and other specific deficiencies should be corrected beforehand.

When possible, both the electrocardiogram and renal and hepatic function should be monitored throughout treatment. Dosage must be reduced should abnormalities occur.

Use in pregnancy

Safe use in pregnancy has not been established. However, because it is potentially fatal, visceral leishmaniasis should always be treated without delay.

Adverse effects

Electrocardiographic changes are dose-dependent and usually reversible; typically, T-wave inversion and prolongation of the Q-T interval precede serious dysrhythmias.

Hepatic and renal function may be impaired.

Headache, malaise, dyspnoea, skin rashes, facial oedema and abdominal pain are also occasionally associated with treatment.

Storage

Ampoules should be stored in well-closed containers, protected from light. It should be noted that antimonial compounds are polymers that may deteriorate with age.

Pentamidine

Group: antiprotozoal agent

Powder for injection 200 mg, 300 mg of pentamidine isetionate

General information

A stable diamidine compound with antiprotozoal activity which must be admini-

stered parenterally since it is not absorbed reliably from the gastrointestinal tract. It does not enter the cerebrospinal fluid. Detectable amounts remain selec-

tively bound in the liver and kidney for many months. Only a small fraction is excreted unchanged in the urine.

Clinical information

Uses

Treatment of:

- visceral leishmaniasis in patients who are unresponsive to — or intolerant of — antimony compounds
- cutaneous leishmaniasis, diffuse cutaneous leishmaniasis and mucocutaneous leishmaniasis due to *L. aethiopica*
- cutaneous leishmaniasis due to *L. guyanensis*
- mucocutaneous leishmaniasis due to *L. braziliensis* unresponsive to antimony compounds.

Dosage and administration

The powder should be reconstituted with "water for injection".

Deep intramuscular injection is preferred. Intravenous infusions must be delivered over a period of not less than 60 minutes to avert the risk of cardiovascular collapse.

All doses, which are weight-related, are suitable for both adults and children.

Visceral leishmaniasis

Injection of 4 mg/kg three times a week for 5 to 25 weeks, or longer, until no parasites are detected in two consecutive splenic aspirates taken 14 days apart.

Cutaneous leishmaniasis (*L. aethiopica* and *L. guyanensis*)

Injection of 3–4 mg/kg once or twice a week until the lesion is no longer visible. Relapse is unusual.

Diffuse cutaneous leishmaniasis (*L. aethiopica*)

Injection of 3–4 mg/kg once a week, continued for at least 4 months after parasites are no longer detectable in slit-skin smears. Relapse frequently occurs during the first few months before immunity is established.

Mucocutaneous leishmaniasis (*L. braziliensis* and *L. aethiopica*)

Injection of 4 mg/kg three times a week for 5 to 25 weeks, or longer, until the lesion is no longer visible.

Contraindications

- Known hypersensitivity.
- Severe renal impairment.

Precautions

Because of the risk of hypotension and syncope all patients should remain supine and under observation for at least 30 minutes after each injection.

When possible, blood pressure, full blood count and serum creatinine should be monitored at regular intervals throughout treatment and blood glucose concentrations should be monitored daily.

In immunodeficient patients treatment may need to be interrupted or discontinued should acute deterioration of bone marrow, renal or pancreatic function occur.

Use in pregnancy

Use in pregnancy can induce abortion. However, because it is potentially fatal, visceral leishmaniasis should always be treated without delay.

Adverse effects

Mild nephrotoxicity occurs frequently, and is usually completely reversible.

Acute hypotension and syncope are common after rapid i.v. injection.

Pentamidine (continued)

Pancreatic damage results initially in hypoglycaemia due to excessive insulin release. Subsequent insulin insufficiency may lead to permanent insulin-dependent diabetes.

Other adverse effects include hypocalcaemia, gastrointestinal effects, confusion, hallucinations, cardiac dysrhythmias, local induration and, occasionally,

sterile abscess. Rarely, thrombocytopenia, leukopenia, abnormal hepatic function tests and Stevens-Johnson syndrome have been reported.

Storage

Vials of dry powder should be stored below 30 °C. Dilute solutions should be stored between 2 and 8 °C and any unused portion should be discarded within 24 hours of preparation.

Amphotericin B

Group: antiprotozoal agent

Powder for injection 50 mg in vial

General information

A lipophilic polyene antibiotic which is also active against *Leishmania* spp and certain fungi. Since it is poorly absorbed from the gastrointestinal tract it must be administered parenterally.

It is extensively bound to lipoproteins, but it enters serous cavities and crosses the placental barrier. It is excreted unchanged in the urine over a period of several weeks.

Clinical information

Uses

Treatment of visceral and mucocutaneous leishmaniasis unresponsive to pentavalent antimony compounds.

Dosage and administration

Amphotericin B is a highly toxic substance that should be used only under experienced medical supervision. It must always be administered by slow intravenous infusion, when possible via a central venous catheter.

Administration of 5 mg of hydrocortisone sodium succinate one hour before infusion may reduce the severity of acute reactions, particularly chills, fever and vomiting.

Infusion fluids should be freshly prepared by dissolving 50 mg in 10 ml of sterile water and making up to 500 ml with 5% glucose to give a final concentration of 100 µg of amphotericin B/ml. Solutions containing electrolytes or preservatives are incompatible since they promote precipitation.

For adults, a starting dose of 5 to 10 mg is incremented by 5 to 10 mg daily to the maximum of 0.5 to 1 mg/kg. This is then administered on alternate days. A total cumulative dose of 1–3 g is usually required.

Contraindications

- Known hypersensitivity.

Precautions

Close medical supervision is required throughout treatment.

Renal function and serum potassium should be closely monitored when high doses are administered.

A high fluid intake should be maintained. Potassium supplements may be required to compensate for urinary losses. Dosage must be reduced if renal function deteriorates substantially and particularly if serum creatinine levels rise by over 50%. Infusions of an osmotic diuretic such as mannitol may then be of value.

The blood count should be monitored at regular intervals since bone marrow depression supervenes frequently. Occasionally, blood transfusion becomes necessary.

Use in pregnancy

Safe use during pregnancy has not been established. Amphotericin B should be used only when the need of the mother outweighs the risk of harm to the fetus.

Adverse effects

Chills, fever and vomiting are frequent during infusion and anaphylaxis, flush-

ing, muscle and joint pains, headache and anorexia may also occur. They are often most marked in the first days of treatment.

Deterioration of renal function, which may be only partially reversible, must be anticipated.

Progressive normochromic anaemia may indicate bone-marrow depression. Selective leukopenia and thrombocytopenia are less common.

Nerve palsies, impaired vision, tinnitus and difficult micturition have also been reported.

Overdosage

Large doses may result in anuria, dysrhythmias, cardiac arrest, hypotension, visual disturbances and convulsions. Treatment is symptomatic. Amphotericin B cannot be removed by haemodialysis.

Storage

Vials should be kept in tightly closed containers, protected from light.

Malaria

Malaria is endemic in some 90 countries in Africa, Asia, Oceania and Central and South America, and in the island of Hispaniola in the Caribbean. It has recently been estimated that 300–500 million cases occur each year. In its socio-economic impact, malaria is the most important of the transmissible parasitic diseases.

Types of malaria

Human malaria, which is transmitted by anopheline mosquitos (and rarely by congenital transmission, transfusion of infected blood or use of contaminated syringes among drug users), is caused by four species of plasmodial parasites. *Plasmodium vivax* is the most extensively distributed and causes much debilitating disease. *P. falciparum*, which is also widespread, results in the most severe infections and is responsible for nearly all malaria-related deaths. *P. ovale*, which is mainly confined to Africa, is less prevalent, while *P. malariae*, which causes the least severe but most persistent infections, also occurs widely.

Sporozoites produced in the mosquito vectors from sexual forms of the parasite migrate to the salivary glands. When injected into the human bloodstream they rapidly penetrate the parenchymal cells of the liver where they transform and grow into large tissue schizonts containing considerable numbers of merozoites (tissue schizogony). These begin to rupture after 5 to 20 days, according to the species, and the released merozoites invade circulating erythrocytes. The subsequent rapid intraerythrocytic multiplication of the merozoites (blood schizogony) culminates in the rupture of the host cells, the release of another generation of merozoites and the cyclical invasion of further erythrocytes which, in turn, are destroyed. The destruction of red blood cells and the release of the parasites' waste products produce the episodic chills and fever that characterize the disease. Because some merozoites develop into male or female gametocytes the host becomes a reservoir of infection for mosquitos and completion of the transmission cycle is assured.

Certain tissue forms of *P. vivax* and *P. ovale* which persist in the liver for many months and even years (hypnozoites) are responsible for the relapses characteristic of these forms of malaria. Such latent forms are not generated by *P. falciparum* or *P. malariae*. Recrudescence of these infections results from persisting blood forms in inadequately treated or untreated patients.

Clinical manifestations

The clinical response to infection depends both on the species of the parasite and on the immunological status of the patient. Non-immune travellers to malarious areas risk severe attacks. Acute malaria also occurs where exposure is limited or seasonal and where the collective immunity is relatively low. In these circumstances it can occur in epidemic proportions and affect all age groups in the community. Acute falciparum malaria is a potentially fatal disease causing prolonged, irregular high fever, intense headache and vomiting. Severe infection, associated with intense parasitaemia, frequently gives rise to hyperpyrexia, convulsions, stupor, collapse, copious vomiting and diarrhoea, haemolytic anaemia, and jaundice. Complications include cerebral malaria (characterized by confusion, convulsions and rapidly progressive coma), hypoglycaemia, septicaemia, pneumonia, pulmonary oedema, acute renal failure and massive haemolysis. Chronic or repeated infection often leads to splenomegaly and progressive anaemia. Splenic rupture is a dangerous complication of vivax malaria, and *P. malariae* infection occasionally gives rise to a fatal nephrotic syndrome.

Pregnant women, if untreated, are at particularly high risk of death from falciparum malaria, especially where transmission is intermittent. In holoendemic areas they are partially protected by a measure of immunity. This reduces the risk of congenital infection, but it does not protect the placenta which, particularly in primigravidae, can harbour large numbers of malaria parasites. The fetus is thus inevitably exposed to the effects of placental insufficiency.

Largely as a result of passive transfer of maternal antibodies across the placenta, infants born to immune mothers living in

holoendemic areas are unlikely to acquire malaria for several months after birth. Thereafter, they risk death from severe and recurrent acute attacks during infancy and early childhood. From the age of five until adulthood the severity and frequency of these attacks decrease as immunity develops.

Except among pregnant women, severe malaria is infrequent in adults who have always lived in areas of high transmission.

Prevention

Hopes that malaria could be eradicated by the systematic use of insecticidal sprays and antimalarial drugs have been abandoned. The emergence of vectors resistant to widely used insecticides and of parasites resistant to first-line drugs has resulted both in rising attack rates in many endemic areas and in the need to resort to more costly chemotherapeutic agents associated with greater toxicity.

Systematic insecticidal spraying is often too costly to be used in the rural areas where it is most needed. However, where it can be afforded, it is often necessary to use recently developed, and hence relatively expensive, compounds such as bendiocarb, pirimiphos-methyl, chlorphoxim and synthetic pyrethroids. Destruction of mosquito breeding sites by land drainage schemes and biological control using antilarval parasites (such as *Bacillus thuringiensis* H14 and *B. sphaericus*) or larvivorous fish (such as *Gambusia* spp) can sometimes reduce dependence upon insecticidal chemicals, but the potential of these methods is limited.

Emphasis is now placed upon prompt diagnosis and treatment of the disease, and upon targeted use of antimalarial drugs with a view to reducing the risk of emergence of drug resistance and unnecessary drug-induced toxicity. Routine prophylaxis is now generally reserved exclusively for pregnant women, special groups, such as labour teams and military personnel living in closed communities, and non-immune visitors to endemic areas. Efforts are consequently being intensified to teach communities and individuals at risk how to reduce contact with mosquitos and, in particular, to encourage the use of bednets, preferably impregnated with safe, long-lasting insecticides such as permethrin or deltamethrin.

Vaccines against sporozoites and other forms of the parasite are under development, and one such vaccine, SPf66, which was developed in Colombia, is currently undergoing extensive clinical trials.

Antimalarial drugs¹

Various comprehensive classifications of antimalarial drugs have been proposed.² The table provides a simplified summary of information necessary for understanding routine approaches to treatment and prophylaxis. In practice, the choice of treatment is influenced not only by the intrinsic properties of the drug but also by the degree to which the locally occurring parasites have developed specific patterns of drug resistance.

Class	Drug	Biological activity	
		Blood schizontocide	Tissue schizontocide
4-Aminoquinolines	chloroquine	++	0
Arylaminoalcohols	quinidine	++	0
	quinine	++	0
	mefloquine	++	0
	halofantrine	++	0
Phenanthrene methanol			
Artemisinin and its derivatives	artemisinin	++	0
	artemether	++	0
	artesunate	++	0
Antimetabolites	proguanil	+	+
	pyrimethamine	+	0
	sulfadoxine	+	0
	sulfalene	+	0
	dapsone	+	0
Antibiotics	tetracycline	+	+
	doxycycline	+	+
	minocycline	+	+
8-Aminoquinoline	primaquine	0	+

¹ For further information, see *Practical chemotherapy of malaria. Report of a WHO Scientific Group*. Geneva, World Health Organization. 1990 (WHO Technical Report Series, No. 805).

² See for example:

Bruce-Chwatt LJ et al. *Chemotherapy of malaria*. 2nd revised ed. Geneva, World Health Organization, 1986.

Warhurst DC. Chemotherapeutic agents and malaria research. In: Taylor AE, Muller R, eds. *Chemotherapeutic agents in the study of parasites*. Oxford, Blackwell, 1973.

Blood schizontocides

These are the mainstay of the treatment of acute malaria and some are also used for prophylaxis. They include the 4-aminoquinolines (chloroquine), the related arylaminoalcohols (mefloquine and quinine), the phenanthrene methanol halo-fantrine, and artemisinin and its derivatives. They suppress the disease by destroying the asexual blood forms of the parasites but, because they are not active against intrahepatic forms, they do not eliminate infections by *P. vivax* and *P. ovale*, whose intrahepatic forms can remain latent for months or even years.

These schizontocidal properties are shared by various anti-metabolites (including pyrimethamine, sulfonamides and sulfones) and by some antibiotics (particularly tetracyclines). Because they act more slowly, these substances are of little value when used alone. However, some antimetabolites act synergistically in combination: for example, pyrimethamine in combination with a sulfonamide or sulfone is a potent blood schizontocide. The tetracyclines are used primarily as adjuncts to quinine where multiple-drug-resistant *P. falciparum* is prevalent.

Tissue schizontocides

Proguanil is a "pro-drug" which is transformed in the liver into its active form, cycloguanil. This is described as a causal prophylactic agent since it is active against pre-erythrocytic intrahepatic forms, particularly of *P. falciparum*. The latent persistent liver forms of *P. ovale* and *P. vivax* are unresponsive.

Primaquine, unlike proguanil, is effective in eliminating the latent liver forms of *P. ovale* and *P. vivax* which persist after suppressive treatment with chloroquine. However, because of its toxicity, and in particular the risk of haemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, it is not suitable for prophylaxis.

The tetracyclines are active against tissue forms as well as blood forms of *P. falciparum*. This effect has limited clinical application, however, because of their innate toxicity, particularly in the fetus and young child, as well as their suppressive effect on the normal bowel flora. None the less,

doxycycline has been used for short-term prophylaxis in non-pregnant adult travellers to areas of high multiple-drug resistance.

Drugs for restricted use

Halofantrine, a phenanthrene methanol derivative known to have blood schizontocidal activity, should be reserved for use in areas where multiple-drug-resistant falciparum malaria is prevalent. Strict governmental control of its importation, distribution and utilization is recommended. It has no place in malaria control programmes because of its high cost, its variable bioavailability and cross-resistance to mefloquine. Furthermore, cases of serious cardiotoxicity have recently been reported. However, it may be used on an individual basis in patients known to be free from heart disease in areas where multiple-drug resistance is prevalent and no other antimalarial is available.

Artemisinin and its derivatives¹ are the most rapidly acting of all antimalarial drugs and they offer particular advantages in the management of severe and multiple-drug-resistant malaria. In order to restrict their use and to limit as far as possible the development of resistance, strict governmental regulation of importation, distribution and utilization is necessary. In areas where other antimalarials remain effective, the use of the artemisinin group of drugs is not currently recommended.

Chemotherapy of acute uncomplicated malaria

The successful management of patients with acute uncomplicated malaria demands the observance of several points of principle:

- Whenever possible, the diagnosis should be confirmed before treatment by microscopic examination of blood smears. However, in areas of intense transmission where most children are asymptomatic carriers, microscopy is of little value

¹ For further information, see *The role of artemisinin and its derivatives in the current treatment of malaria (1994–1995). Report of an Informal Consultation, Geneva, 27–29 September 1993*. Geneva. World Health Organization, 1993 (unpublished document WHO/MAL/94.1067; available on request from Malaria Control. Division of Control of Tropical Diseases, World Health Organization, 1211 Geneva 27, Switzerland). Further recommendations on the use of these drugs will be issued as required.

in diagnosing uncomplicated primary attacks and should be reserved for diagnosing treatment failures and severe and complicated disease.

- Drugs used to treat falciparum malaria must always be selected with due regard to the prevalence of specific patterns of drug resistance.
- Patients should always be supervised to ensure that they swallow the prescribed tablets. If they are subsequently vomited, the same dose must immediately be readministered.
- Patients not at risk of reinfection should be re-examined several weeks after treatment for signs of recrudescence, which may result from inadequate chemotherapy or survival of persistent hepatic forms.
- A careful medical history should be taken to determine whether other antimalarial drugs have already been given. Patients who have received treatment within the previous 24–36 hours may be at risk of adverse drug interactions and should be monitored carefully.

Chloroquine, administered orally, is a well-tolerated, safe, inexpensive and rapidly acting blood schizontocide. It should be used to treat malaria wherever the parasites remain susceptible. *P. ovale* and *P. malariae* still remain fully sensitive to chloroquine. However, chloroquine-resistant strains of *P. falciparum* are now widespread in south-east Asia and in parts of the Indian subcontinent, South America, Africa and Oceania. Strains of *P. vivax* resistant to chloroquine have been reported from Indonesia and Papua New Guinea.

If subsequent relapse occurs in *P. ovale* and *P. vivax* infections primaquine should be administered, after a second course of chloroquine, to eliminate the intrahepatic infection.

The combination of pyrimethamine with a sulfonamide (either sulfadoxine or sulfalene) has been used successfully in areas of high chloroquine resistance. However, resistance to these combinations is now widespread, particularly in south-east Asia and South America, and has also been reported in east and central Africa.

The blood schizontocide mefloquine remains effective against the blood forms of all malaria parasites, except in certain areas of resistance in Cambodia, Myanmar and Thailand. No parenteral preparations are currently available, and it is thus suitable only for patients who can take drugs by mouth. It is generally well tolerated although a few reports of psychotic reactions and impaired coordination have been reported. However, because of the danger of the emergence of mefloquine-resistant strains of *P. falciparum* and because of its potential toxicity, it should be used only following either microscopic or careful clinical diagnosis of *P. falciparum* infections that are known or strongly suspected to be resistant to chloroquine or sulfadoxine/pyrimethamine.

Quinine, given orally, should be reserved for infections likely to be unresponsive to other drugs. However, radical cure requires prolonged courses of treatment, which are associated with poor compliance and hence favour the development of resistance. Resistance to quinine was, until recently, rare, but the prevalence of resistant strains is now increasing in parts of south-east Asia and South America. Tetracycline, which is an effective oral schizontocide, should be given in combination with quinine except in pregnant women and children under 8 years.

In certain cases all the above treatment regimens are failing because of the emergence of drug-resistant strains. In these circumstances preparations of artemisinin or its derivatives offer the only prospect of cure. In uncomplicated cases of falciparum malaria oral artemisinin preparations should be used in combination with a single dose of mefloquine — even where mefloquine resistance is emerging — for 3 successive days. If, for any reason, the oral artemisinin compounds have to be used alone, they should be given for a minimum of 5 successive days.

Oral artesunate in a total dose of 10 mg/kg has given cure rates of over 90% among patients assessed 28 days after completion of treatment. Equivalent results have been obtained in Viet Nam with oral artemisinin (total dose of 50 mg/kg). Studies

are now in progress with oral artemether and other related compounds, but appropriate dosage regimens have yet to be established.

Chemotherapy of severe falciparum malaria¹

General points of management of patients with severe falciparum malaria include the following:

- Patients should receive the best medical and nursing care available, preferably in an intensive care unit.
- Whenever possible, the diagnosis should be confirmed before treatment by microscopic examination of blood smears and patients should be monitored throughout treatment by blood microscopy and other laboratory examinations.
- Drugs must always be selected with due regard to the prevalence of specific patterns of drug resistance.

Supportive therapy is directed mainly to reducing hyperpyrexia, correcting hypoglycaemia, controlling convulsions and bacterial infection, and maintaining an adequate fluid and electrolyte balance. Severely anaemic patients may need blood transfusion. If adequate facilities are available, exchange transfusion can be beneficial when there is intense parasitaemia. Peritoneal dialysis or haemodialysis can be life-saving if acute renal failure supervenes. Corticosteroids have no place in the management of these conditions.

Because of the need for a rapid response, severe falciparum malaria should be treated initially by slow intravenous infusion of quinine. Where quinine is not available, its stereoisomer, quinidine, may be used but intensive cardiovascular monitoring is then required. Where it is impractical to set up an infusion, quinine may safely be administered intramuscularly. However, precautions must be taken to minimize the risk of muscle necrosis and abscess formation.

Notwithstanding concerns regarding cardiotoxicity, chloroquine administered cautiously parenterally in small repeated

¹ For further information, see Gilles HM. *Management of severe and complicated malaria: a practical handbook*. Geneva, World Health Organization, 1991.

doses is safe, and is less locally toxic and more rapidly acting than quinine. It should be used, however, only in areas where there is no expectation of chloroquine resistance and when neither quinine nor quinidine is available.

Parenteral artemether or artesunate is an effective alternative to parenteral quinine for the treatment of severe falciparum malaria, and is preferred in areas where decreased efficacy of quinine has been documented. Recent research suggests that artemisinin suppositories may be comparably effective but this has yet to be confirmed. To ensure radical cure following parenteral treatment with artemether or artesunate, a full therapeutic dose of mefloquine should be given.

Chemoprophylaxis

Approaches to chemoprophylaxis for persons visiting endemic areas are maintained under constant review by the World Health Organization. For recommendations operative in specific countries the reader is referred to the current, annually revised WHO booklet *International travel and health: vaccination requirements and health advice*.

No drug regimen gives assured protection to everybody, and indiscriminate use of existing antimalarials increases the risk of inducing resistance. Chloroquine, which is usually well tolerated at the required dosage, is preferred where *P. falciparum* remains fully sensitive. Either mefloquine or doxycycline may be used in areas where multiple-drug resistance has been reported. The latter should not be used in children under 8 years because of its adverse effects on bone and tooth development. Because of widespread resistance, pyrimethamine is no longer used alone for prophylaxis, and other drugs are associated with too great a risk of toxic effects to be used in this way even when they are administered on a short-term basis.

Prophylaxis should be continued for at least 4 weeks after the last risk of exposure. Risk of recrudescence of *P. falciparum* and *P. malariae* infections is then remote. Relapses of *P. vivax* or *P. ovale* malaria may occur even after the 4-week period and

should be treated with a combination of chloroquine and primaquine.

Travellers to areas where drug-resistant strains of *P. falciparum* are known to be endemic should be advised to take all practicable measures to protect themselves against mosquito bites. Such measures should include the use of bednets. Insect repellents such as diethyltoluamide are effective and safe if used in accordance with recommendations. Excessive application of highly concentrated preparations to small children, however, has occasionally resulted in toxic encephalopathy.

In certain areas, where the risk of transmission is particularly high, and when it can be anticipated that medical attention will not be readily available, non-immune travellers should carry a "stand-by" supply of an appropriate antimalarial to assure prompt treatment of presumptive symptoms of a malarial attack.

Drugs used during pregnancy

Pregnant women who have little or no immunity are at increased risk of acute complications of malaria, including anaemia.

Effective antimalarial prophylaxis can markedly reduce the incidence of low birth weight, stillbirths and neonatal deaths among infants born to primigravidae living in endemic areas. The benefits are less marked among multigravidae; it is possible that protection during one pregnancy may increase susceptibility to malaria in the next.

Where *P. falciparum* remains sensitive to chloroquine, women should take chloroquine prophylactically throughout pregnancy. It may also be used safely at full dosage to treat chloroquine-sensitive infections. Proguanil can also be safely taken during pregnancy in areas where *P. falciparum* remains sensitive and combinations of chloroquine and proguanil may be effective. The safety of mefloquine during the first trimester has not been established. It should be used only if alternative drugs are either not available or unlikely to be effective and only when it is impracticable for the woman to leave the

endemic area. The effectiveness of pyrimethamine has been compromised by widespread resistance and combinations of pyrimethamine and a sulfonamide are too toxic to be used prophylactically. Increasingly, reliance will have to be placed upon avoidance of mosquito contact, prompt diagnosis of infection and treatment with quinine.

Quinine is the only widely available drug that is accepted as suitable for treating chloroquine-resistant infections during pregnancy. Mefloquine has now been shown to be safe and effective for therapeutic purposes during the second and third trimester. The use of artemisinin and its derivatives for treatment during pregnancy remains under investigation, but these preparations should not be withheld when they could be life-saving to the mother.

Chloroquine

Group: antimalarial agent

Tablet 100mg, 150mg, 300mg base (as phosphate or sulfate)

Syrup 50mg base (as phosphate or sulfate) in 5ml

Injection 50mg, 100mg base (as phosphate or sulfate) per ml in 2-ml ampoule
[chloroquine base 150mg is equivalent to chloroquine sulfate 200mg or chloroquine phosphate 250mg]

General information

Policy regarding the use of this drug as an antimalarial must be determined nationally since in many areas *P. falciparum* is now resistant to chloroquine. It may still be used effectively, however, in areas where low-grade *P. falciparum* resistance is reported, especially in persons likely to have acquired a significant degree of immunity, and also wherever *P. vivax* is the predominant parasite.

Chloroquine is a 4-aminoquinoline which has marked, rapid schizontocidal activity against blood forms of *P. ovale* and *P. malariae* and against susceptible strains of *P. vivax* and *P. falciparum*. It is also gametocytocidal against *P. vivax*, *P. ovale* and *P. malariae* and immature *P. falciparum*. It is not active against intrahepatic forms.

Absorption is efficient following oral administration and peak plasma concentrations occur within 2–3 hours. The drug and its metabolites can be detected in the plasma for up to 2 months and in the urine for up to 4 months after a single dose.

Clinical information

Uses

Treatment of acute malarial attacks:

- *P. malariae* and susceptible *P. falciparum* infections are eliminated by treatment with chloroquine alone.

- When there is little or no likelihood of immediate reinfection, elimination of naturally acquired *P. vivax* and *P. ovale* infections requires subsequent administration of primaquine to eliminate persistent intrahepatic forms (hypnozoites). These forms do not occur in infection acquired congenitally, or from transfusions or other contaminated injections.

Chloroquine is also used for prophylaxis for pregnant women and non-immune individuals at risk.

Dosage and administration

All dosages are described in terms of the base.

Treatment

Oral administration

To avoid nausea and vomiting chloroquine should be administered after meals. If part or all of a dose is vomited, the same amount must immediately be readministered.

Adults, including pregnant women, and children:

Total dose: 25mg/kg given over 3 days.
Day 1: 10mg/kg, followed by 5mg/kg 6–8 hours later.

Days 2 and 3: 5mg/kg in a single dose.

A more practical, but pharmacokinetically inferior, regimen is used in many areas:

Days 1 and 2: 10mg/kg.

Day 3: 5mg/kg.

The above regimens are sufficient to eliminate susceptible *P. falciparum* infections since effective antimalarial plasma concentrations are sustained for several weeks.

Parenteral administration

Parenteral administration of chloroquine should be considered when there is no expectation of resistance, when the patient is unable to take drugs orally and when neither quinine nor quinidine is available. Excessively rapid administration results in toxic peak plasma concentrations and a danger of fatal cardiovascular collapse.

Adults and children: the initial dose of 10 mg/kg should be administered over a period of not less than 8 hours, preferably by very slow intravenous infusion. Subsequent infusions of 5 mg/kg should be administered every 8 hours until a total dose of 25 mg/kg has been given.

Infusions should be discontinued as soon as the patient is able to take chloroquine by mouth.

Where facilities for intravenous infusion are not available chloroquine can be administered by intramuscular or subcutaneous injection at a dosage of 2.5 mg/kg every 4 hours or 3.5 mg/kg every 6 hours until a total of 25 mg/kg has been given.

Prophylaxis

Adults including pregnant women: 300 mg weekly.

Children: 5 mg/kg weekly.

This regimen has been employed effectively even in areas of marginal resistance. However, it must be started 1 week before exposure and be maintained until after delivery in pregnant women and for at least 4 weeks after the last risk of exposure in the case of non-immune individuals. This is sufficient to

ensure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, whose residual hepatic forms survive.

Contraindications

- Known hypersensitivity.
- Chloroquine should not be taken for prophylaxis by patients with a history of epilepsy.

Precautions

If the condition of the patient deteriorates after administration of chloroquine, resistance must be suspected and quinine must be administered intravenously as an emergency measure.

Use in pregnancy

There is no evidence that chloroquine is harmful in prophylactic doses during pregnancy. Because of the susceptibility of pregnant women to falciparum malaria, it should be used at the recommended dosage for both prophylaxis and treatment wherever chloroquine-sensitive malaria is prevalent.

Adverse effects

Serious adverse effects are rare at the dosages used for malaria, but pruritus, which may be intolerable, is common among Africans and has also been reported from South and Central America and south-east Asia. It can often be alleviated by calamine lotion but if it compromises compliance it may be necessary to use an alternative antimalarial.

Transient headaches and gastrointestinal symptoms are occasionally troublesome. In susceptible individuals, severe attacks of acute intermittent porphyria and of psoriasis may be precipitated. The former may simulate an attack of cerebral malaria. When the diagnosis is in doubt the urine should be tested for porphobilinogen.

Chloroquine (continued)

Where self-medication is common and chloroquine is used without supervision to treat virtually any febrile condition, chloroquine abuse has been claimed to be a common cause of cardiac atrio-ventricular block. These patients are also at risk of developing chloroquine retinopathy.

Irreversible visual impairment resulting from accumulation of chloroquine in the retina is a recognized complication of long-term, high-dosage therapy. Total lifetime exposure to chloroquine should not exceed 100g of the base. Retinopathy has rarely, if ever, resulted from doses currently recommended for malaria prophylaxis.

Overdosage

Acute chloroquine poisoning is often fatal: oral doses as low as 50 mg base/kg can be lethal. Nausea, vomiting and drowsiness occur rapidly and are followed by slurring of speech, agitation, breathlessness due to pulmonary oedema, convulsions, coma, impaired vision and cardiac dysrhythmias.

If the patient is seen within a few hours of the event, emesis must be induced or gastric lavage undertaken as rapidly as possible. Otherwise, treatment is symptomatic and is directed particularly to sustaining cardiovascular and respiratory function. Diazepam may help to control convulsions.

Storage

Tablets and syrup should be kept in well-closed containers, protected from light and moisture. Chloroquine injection should be protected from light.

Quinine

Group: antimalarial agent

Tablet 200 mg, 300 mg base (as sulfate)

Injection 150 mg, 300 mg base (as dihydrochloride) per ml in 2-ml ampoule

[quinine anhydrous base 100 mg is equivalent to 122 mg of quinine

hydrochloride dihydrate or quinine dihydrochloride or 121 mg of quinine sulfate dihydrate]

General information

Quinine, an alkaloid derived from the bark of the cinchona tree, is a blood schizontocidal agent that is more toxic than chloroquine. Its use has become re-established because of the widespread emergence of chloroquine-resistant — and, more recently, multiple-drug-resistant — strains of malarial parasites.

Quinine is rapidly absorbed when taken orally and peak plasma concentrations are attained after 1–3 hours. It is highly

protein-bound but it readily crosses the placental barrier and small amounts penetrate into the cerebrospinal fluid. It is metabolized in the liver, has a plasma half-life of 10 hours and is subsequently excreted in the urine, mainly as hydroxylated metabolites.

Clinical information

Uses

Quinine is used in the treatment of falciparum malaria in areas of multiple-drug-resistant *P. falciparum*.

It is administered parenterally to patients with severe or complicated malaria who cannot take drugs by mouth because of coma, convulsions or vomiting.

It is administered orally to less seriously ill patients with infections likely to be resistant to chloroquine or mefloquine, sometimes in combination with pyrimethamine/sulfadoxine or a tetracycline.

Dosage and administration

Unless otherwise stated, all dosages are described in terms of the base. However, most dose-finding studies for parenteral administration have been carried out with the salt quinine dihydrochloride.

Intravenous administration

Adults and children: an initial dose of 16.4mg (equivalent to 20mg of dihydrochloride)/kg is infused over 4 hours followed by 8.2mg (equivalent to 10mg of dihydrochloride)/kg every 8 hours in adults and every 12 hours in children. However, the initial dose should be halved if the patient has received quinine, quinidine or mefloquine during the previous 12–24 hours. The maintenance doses should be reduced threefold in patients with impaired renal function. Pulse and blood pressure should be closely monitored during administration and the rate of infusion reduced if dysrhythmias occur.

The required dose, diluted preferably in 5% (w/v) glucose solution to counteract hypoglycaemia, is given in a total volume of 5–10ml/kg by infusion into a large vein. In the absence of glucose, physiological saline may be used. This method of administration minimizes the danger of severe hypotension and subsequent respiratory collapse.

Where facilities for intravenous infusion do not exist, quinine can be

administered intramuscularly in the same dosage. The required dose should be divided equally between two sites, one in each anterior thigh. However, in some cases, muscle necrosis and sterile abscesses have been reported.

Parenteral treatment should be discontinued as soon as the patient is able to take quinine orally. A radical cure should then be effected using pyrimethamine/sulfadoxine, mefloquine or oral quinine combined with tetracycline (except in pregnant women and children under 8 years), according to the susceptibility of the parasite.

When quinine is not available, quinidine may be administered. An initial loading dose of 15mg/kg in physiological saline is given over 4 hours. This is followed by a maintenance dose of 7.5mg/kg infused every 8 hours until the patient is able to take quinidine by mouth. Pulse, blood pressure and electrocardiographic monitoring must be undertaken.

Oral administration

Quinine should be given orally for the treatment of uncomplicated multi-drug-resistant falciparum malaria and to complete the treatment of patients with severe or complicated malaria, who are initially treated parenterally. If part or all of a dose is vomited within 1 hour, the same amount must be readministered immediately.

Adults: 500mg (equivalent to quinine sulfate dihydrate 600mg) every 8 hours for 3, 7 or 10 days.

Children: 8.2mg (equivalent to quinine sulfate dihydrate 10mg)/kg every 8 hours for 3, 7 or 10 days.

The duration of treatment depends on the local susceptibility of *P. falciparum* to quinine and on whether treatment is combined with pyrimethamine/sulfadoxine or tetracycline.

Quinine (continued)

Contraindications

- Known hypersensitivity.

Precautions

Whenever possible, blood glucose should be monitored throughout treatment. Both the disease itself and the administration of quinine may promote insulin secretion and induce hypoglycaemia. This may require correction by infusion of a 20% or 50% glucose solution. In patients who are seriously ill, treatment should always be accompanied by continuous infusion of carbohydrates.

Haemolysis can occasionally be severe enough to warrant discontinuation of quinine treatment if an alternative is available.

Use in pregnancy

Quinine should not be withheld during pregnancy, despite its alleged abortifacient properties at high dosage, since it safeguards the life of the mother.

Attention should be given to the considerable risk of hypoglycaemia in pregnant women with severe malaria.

Adverse effects

Serious reactions are infrequent provided the plasma concentration is not allowed to rise above 15 mg/l.

Signs of mild to moderate cinchonism (tinnitus, headache, blurred vision, altered auditory acuity, nausea and diarrhoea) often supervene after the third day of treatment. These rarely, if ever, constitute grounds for withdrawal. However, if, as a result of non-compliance, quinine has to be withdrawn prematurely, tetracycline must be administered for a further 7 days.

Idiosyncratic reactions can also occur, but they are uncommon. They include pruritic, urticarial or erythematous rashes, subcutaneous or submucous haemorrhage, and oedema of the eyelids, mucous membranes and lungs. Haemoglobinuria and asthma are rare.

Hypoglycaemia should be treated promptly with supplementary glucose.

Renal damage, culminating in acute renal failure and anuria, is a frequent terminal event in malaria. Rarely, anuria is a consequence of blackwater fever, a syndrome comprising massive haemolysis, haemoglobinaemia and haemoglobinuria. Although this has been ascribed in the past to inadequate quinine therapy, the supporting evidence is insecure. Blackwater fever certainly occurs in patients who have not received treatment with quinine.

Dose-related adverse effects are largely limited to the cardiovascular, gastrointestinal and central nervous systems. They usually arise from excessive infusion, but quinine accumulation can result from oral administration.

Overdosage

The most frequently encountered signs of overdosage are:

- Tinnitus, decreased auditory acuity and vertigo. Permanent deafness has resulted from exposure to toxic doses.
- Amblyopia, constricted visual fields, diplopia and night blindness. Recovery is slow but usually complete.
- Quinidine-like effects resulting in hypotension, conduction disturbances, anginal symptoms and ventricular tachycardia.
- Hypoglycaemia.
- A local irritant effect on the gastrointestinal tract resulting in nausea, vomiting, abdominal pain and diarrhoea.

A single oral dose greater than 3g is capable of causing serious and potentially fatal intoxication in adults, preceded by depression of the central nervous system and seizures. Much smaller doses can be lethal in children.

Dysrhythmias, hypotension and cardiac arrest can result from the cardiotoxic action and ocular toxicity can lead to blindness.

Emesis should be induced and gastric lavage undertaken as rapidly as possible. Activated charcoal should then be administered.

Supportive measures, to be employed as necessary, include ventilation, and symptomatic treatment of dysrhythmias, cardiac failure and convulsions. No specific measures of proven efficacy exist to reduce the toxicity or to promote the excretion of quinine.

Storage

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

Pyrimethamine/sulfadoxine

Group: antimalarial agent

Tablet 25mg of pyrimethamine + 500mg of sulfadoxine

General information

A combination product containing two compounds that act synergistically to inhibit folic acid metabolism: a dihydrofolate reductase inhibitor, pyrimethamine, and a dihydropteroate synthase inhibitor, sulfadoxine. The combination has blood schizontocidal activity against *P. falciparum* and *P. vivax*. The two constituents were first used in combination, following rapid development of resistance to pyrimethamine alone, to treat *P. falciparum* infections unresponsive to chloroquine. Strains of *P. falciparum* and *P. vivax* resistant to this combination are now widespread in many areas.

Both components are efficiently absorbed after oral administration. The plasma half-life of pyrimethamine is about 4 days and that of sulfadoxine about 8 days. Both substances are

ultimately excreted in the urine, pyrimethamine partly as metabolites.

A combination product containing sulfalene instead of sulfadoxine appears to have the same efficacy and adverse effect profile.

Clinical information

Uses

Treatment of acute attacks of malaria caused by susceptible strains of *P. falciparum*:

- in areas where chloroquine is no longer used because of resistance, and
- in patients who have failed to respond satisfactorily to treatment with chloroquine.

Dosage and administration

Adults: pyrimethamine 75mg plus sulfadoxine 1.5g (3 tablets).

Pyrimethamine/sulfadoxine
(continued)

Children:

- 5–10 kg: 0.5 tablet
- 11–20 kg: 1 tablet
- 21–30 kg: 1.5 tablets
- 31–45 kg: 2 tablets.

A single dose usually suffices to eliminate infection, but quinine should additionally be given for 3 days to:

- severely infected patients, in whom quinine may accelerate reduction of parasitaemia and clinical improvement
- non-immune patients at risk of fulminating disease.

Contraindications

- Known hypersensitivity to sulfonamides or pyrimethamine.
- Severe hepatic or renal dysfunction (except when no alternative treatment is available).

Precautions

Patients who develop signs suggestive of sulfonamide or pyrimethamine sensitivity should never receive drugs containing these substances again. These signs include skin rashes, evidence of haemolysis including dark urine and purpura, and presumptive signs of bone-marrow depression such as sore throat and mouth ulcers.

Use in pregnancy

Quinine should be used, whenever possible, to treat chloroquine-resistant malaria during pregnancy. Administration of sulfonamides can induce severe hypersensitivity reactions in pregnant women. They readily cross the placental barrier and their action in displacing bilirubin from protein-binding sites has given rise to concern, based on data derived from premature neonates, that they may provoke

kernicterus. There is no adequate direct evidence, however, that the fetus is at risk.

Adverse effects

Adverse reactions to pyrimethamine are usually dose-related and reversible. Anorexia, abdominal cramps, vomiting, ataxia, tremors, seizures and megaloblastic anaemia due to folic acid deficiency have been reported. Eosinophilic pneumonia may also occur.

Sulfonamide-induced hypersensitivity reactions, although uncommon, can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens–Johnson syndrome) and toxic epidermal necrolysis.

Other infrequent reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Haemolysis occasionally occurs in individuals with glucose-6-phosphate dehydrogenase deficiency.

Pyrimethamine/sulfadoxine is no longer recommended for prophylaxis or treatment of malaria sensitive to chloroquine because serious sulfonamide-induced adverse reactions have been reported to occur with an incidence of 1:5000 to 1:8000 in people taking the drugs prophylactically. No comparable data are available to establish the magnitude of the risk associated with single therapeutic doses.

Drug interactions

Other drugs that interfere with folic acid metabolism (such as trimethoprim and methotrexate) should not be taken concurrently.

Overdosage

High doses of pyrimethamine are potentially fatal. Prominent symptoms of overdosage are anorexia, vomiting and seizures. Induction of emesis or

gastric lavage is of value if undertaken within a few hours of ingestion. Convulsions may be controlled with parenteral diazepam.

Blood dyscrasias, which may be induced by large doses of pyrimetha-

mine, should be treated with calcium folinate.

Storage

Tablets should be kept in well-closed containers, protected from light and moisture.

Primaquine

Group: antimalarial agent

Tablet 7.5mg, 15mg base (as diphosphate)

General information

An 8-aminoquinoline derivative with a potent action against the intrahepatic forms of all human malaria parasites, but which is too toxic to be used routinely for causal prophylaxis. It also has a gametocytocidal effect against all species.

Primaquine is readily absorbed when taken orally. Peak plasma concentrations occur within 1–3 hours and the plasma half-life is about 5 hours. It is rapidly metabolized in the liver and only a small amount is excreted unchanged in the urine.

Clinical information

Uses

- Elimination of intrahepatic forms of *P. vivax* and *P. ovale* (hypnozoites) after standard chloroquine therapy when the risk of subsequent re-exposure is absent or slight. In areas of intense transmission, blood schizontocides alone are used to treat relapses and reinfections.
- Elimination of gametocytes of *P. falciparum* following routine therapy

with a blood schizontocide, particularly in areas where there is a potential for reintroduction of malaria.

Dosage and administration

All dosages are described in terms of the base.

Radical treatment of *P. vivax* and *P. ovale* malaria

Adults: 0.25mg/kg or 15mg daily for 14 days following standard chloroquine therapy or, if glucose-6-phosphate dehydrogenase (G6PD) deficiency is known or suspected, 0.75mg/kg weekly for 8 weeks.

Children over 1 year: 0.25mg/kg daily for 14 days after standard chloroquine therapy.

Gametocytocidal therapy

Adults and children: 0.5–0.75mg/kg in a single dose.

Contraindications

- Pregnancy.
- Age under 1 year.
- Any condition that predisposes to granulocytopenia, including active rheumatoid arthritis and lupus erythematosus.

Primaquine (continued)

Precautions

Blood and urine should be examined periodically for evidence of haemolysis.

Patients should be warned to stop treatment and report immediately to a doctor if they have abdominal pain and become weak or pale, or notice darkening of the urine.

When possible, G6PD deficiency should be excluded before the standard therapeutic dosage for radical treatment of *P. vivax* and *P. ovale* malaria is administered.

Primaquine administered as a gametocytocidal measure in a single dose is usually well tolerated. Prior testing for G6PD deficiency is not required in these circumstances.

Adverse effects

Dose-related gastrointestinal symptoms include anorexia, nausea and abdominal pain.

Acute haemolytic anaemia occurs most frequently in patients with G6PD deficiency. It is usually self-limiting but in severe cases blood transfusion may be necessary.

Methaemoglobinaemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia occur rarely.

Drug interactions

Primaquine should not be administered concurrently with any other drug that is likely to induce haemolysis or bone-marrow depression.

Overdosage

Gastrointestinal symptoms, weakness, methaemoglobinaemia, cyanosis, haemolytic anaemia, jaundice and bone-marrow depression may occur. There is no specific antidote and treatment is consequently symptomatic.

Storage

Tablets should be kept in well-closed containers, protected from light.

Mefloquine

Group: antimalarial agent

Tablet 250mg base (as hydrochloride)

General information

Mefloquine, a 4-aminoquinoline methanol, is a relatively new blood schizonticide which, like chloroquine, is active against the asexual blood stages of all malaria parasites. It is also active against the gametocytes of *P. vivax*, *P. ovale* and *P. malariae*.

Absorption from the gastrointestinal tract is rapid. The compound is almost completely bound to plasma proteins and plasma concentrations decay with a half-life varying from 15 to over 30 days.

Very little of the administered dose is excreted unchanged in the urine.

Clinical information

Uses

- Treatment of uncomplicated attacks of malaria due to multiple-drug-resistant strains of *P. falciparum*.
- Follow-up to quinine treatment for severe and complicated malaria.
- In combination with artemisinin and its derivatives for the treatment of *falciparum* malaria.

- Prophylaxis for travellers to areas with a high prevalence of multiple-drug-resistant *P. falciparum*.

Dosage and administration

All dosages are described in terms of the base.

Treatment

Adults and children: 15mg/kg to a maximum of 1000mg in a single dose.

Prophylaxis

Adults: 250mg weekly.

Children over 15kg: 5mg/kg weekly.

Prophylaxis should be started 1 week before exposure and continued for 4 weeks after last exposure.

Contraindications

- Use of cardioactive drugs, particularly β -adrenoreceptor- and calcium-channel-blocking agents, since mefloquine has been associated with asymptomatic sinus bradycardia.
- Involvement in activities requiring fine coordination and spatial performance, such as flying, or the use of heavy or dangerous equipment.
- History of epilepsy or psychiatric disorders.

Precautions

As yet there is little clinical experience with the use of mefloquine in infants.

Use in pregnancy

Mefloquine should not be used for prophylaxis during pregnancy. Its therapeutic use has now been shown to

be safe during the second and third trimester. However, it should be used in early pregnancy only if alternative drugs are either not available or unlikely to be effective and when it is impracticable for the woman to leave the endemic area.

Adverse effects

Mefloquine is, in general, well tolerated but dose-related adverse effects, including nausea and dizziness, can be severe. Mild to moderate reactions include disturbed sense of balance, vomiting, diarrhoea, abdominal pain and loss of appetite. Other rare effects include headache, bradycardia, rash, pruritus and feeling of weakness. Neurological adverse effects including vertigo, blurred vision and abnormal coordination have been reported, as have psychiatric adverse effects including hallucinations, seizures and psychoses, which may be dose-related.

Drug interactions

Concurrent use of quinine can potentiate the dose-related adverse effects of mefloquine. In general, mefloquine should not be administered within 12 hours of the last dose of quinine.

Overdosage

Induction of emesis and gastric lavage are of value if undertaken within a few hours of ingestion.

Storage

Tablets should be kept in well-closed containers protected from moisture.

Halofantrine

Group: antimalarial agent

Tablet 250 mg of halofantrine hydrochloride

General information

Halofantrine is a phenanthrene methanol which, like mefloquine, is active against the asexual blood stages of all malaria parasites.

Absorption from the gastrointestinal tract is irregular, but peak plasma concentrations usually occur within about 6 hours. Fatty meals increase the bioavailability of halofantrine.

Clinical information

Uses

Use of this drug should be restricted to treatment in a hospital or clinic setting. It should be used only for treatment of acute attacks of multiple-drug-resistant strains of *P. falciparum* malaria following either parasitological or careful clinical diagnosis.

Dosage and administration

Halofantrine should not be administered with food.

Adults and children over 1 year: 24 mg/kg in three divided doses at 6-hour intervals.

Contraindications

- Age under 1 year.
- Pregnancy.
- Family history of congenital prolongation of the Q-T interval.
- Use of other drugs or presence of clinical conditions known to prolong the Q-T interval.
- Pre-existing cardiac disease.
- Treatment with mefloquine during the preceding 3 weeks.

Precautions

Cross-resistance to mefloquine has been reported.

The variable bioavailability of the compound has raised concerns that subtherapeutic blood concentrations might encourage the selection of resistant parasites and that toxic levels could be attained in some patients, particularly if the drug is taken with a fatty meal.

Use in pregnancy

Halofantrine has been shown to be embryotoxic in animal studies. It is therefore contraindicated during pregnancy.

Adverse effects

Cardiotoxicity (prolongation of Q-T intervals) has recently been reported, particularly in patients previously treated with mefloquine.

Ventricular dysrhythmias have occurred, which have sometimes been fatal. These have been particularly associated with higher than recommended doses and recent or concomitant mefloquine administration, and patients with pre-existing prolongation of the Q-T interval or at risk of thiamine deficiency.

Abdominal pain, diarrhoea, pruritus and skin rashes have been reported.

A reversible increase in the levels of hepatic enzymes may also occur.

Overdosage

As yet there is no clinical experience with the treatment of overdosage.

However, immediate induction of emesis or gastric lavage may be of value.

Storage

Tablets should be stored in well-closed containers.

Tetracycline

Group: antimicrobial agent

Capsule or tablet 250mg of tetracycline hydrochloride

General information

Tetracycline is a broad-spectrum antimicrobial which has a potent but slow action against the asexual blood stages of all plasmodial species. It is also active against the primary intrahepatic stages of *P. falciparum*. The closely related substances doxycycline and minocycline share its actions.

Absorption of tetracycline from the gut is always incomplete and can be further impaired by alkaline substances and chelating agents and, particularly, by milk and milk products, and by aluminium, calcium, magnesium and iron salts.

Peak plasma concentrations occur within 4 hours and decay with a half-life of about 8 hours. Excretion is effected primarily by glomerular filtration into the urine. Enterohepatic circulation gives rise to high concentrations in the liver and bile.

Tetracyclines cross the placenta and are excreted into breast milk.

Clinical information

Uses

Tetracycline is employed primarily as a supplement to quinine in the treatment of *P. falciparum* malaria when resistance to quinine has been reported in patients

in whom pyrimethamine/sulfadoxine is contraindicated because of hypersensitivity to sulfonamides.

Because of its slow action tetracycline should never be used alone in the treatment of malaria. It is not suitable for extended prophylactic use, which could promote the development of resistance not only in plasmodial species, but also in a wide variety of susceptible bacteria. However, in non-pregnant adults the related compound doxycycline, 100mg daily, can be used for short-term prophylaxis in areas of high transmission of *P. falciparum* where other drugs are likely to be ineffective.

Dosage and administration

Tetracycline should always be administered orally in the treatment of malaria.

Adults and children over 8 years: 500mg twice daily for 7–10 days.

Contraindications

- Known hypersensitivity to tetracyclines.
- Pre-existing severe hepatic or renal damage. (Doxycycline, which is not excreted significantly in the urine, is preferred in patients with renal impairment.)
- Age under 8 years, since skeletal deposition can result in retardation of bone growth, hypoplasia of dental enamel and permanent brown discoloration of teeth.

Tetracycline (continued)

Precautions

Oesophageal ulceration may be averted if the patient sits or stands up for a few minutes while the tablets are swallowed, and if they are always washed down immediately with a glass of water.

Other symptoms of gastrointestinal irritability can be reduced if tetracycline is taken with a meal, but milk products must be avoided since they reduce absorption.

Tetracycline should be withdrawn if infective diarrhoea occurs. Supra-infection of the bowel with resistant organisms can result in potentially fatal staphylococcal enteritis and pseudo-membranous colitis.

Time-expired tetracycline capsules or tablets should be discarded. Degraded tetracycline has been reported to induce renal dysfunction indistinguishable from the Fanconi syndrome and skin lesions similar to those of systemic lupus erythematosus.

Use in pregnancy

Tetracycline is generally contraindicated in pregnancy. It impairs skeletal calcification in the fetus and can result in abnormal osteogenesis and hypoplasia of dental enamel. However, in regions where *P. falciparum* infections are not reliably responsive to quinine alone, the benefits of concomitant tetracycline therapy can outweigh the risks.

Adverse effects

Gastrointestinal irritation is common, as

is depletion of the normal bowel flora, permitting overgrowth of resistant organisms. Irritative diarrhoea should be differentiated from enteritis due to suprainfection, particularly with coagulase-positive staphylococci, and from pseudomembranous colitis due to *Clostridium difficile*.

Phototoxic reactions and increased vulnerability to sunburn have occurred. Porphyrin-like skin changes and pigmentation of the nails have also been reported.

Pre-existing renal insufficiency may be aggravated. Acute renal failure and transient diabetes insipidus have been reported.

Transient depression of bone growth is largely reversible, but discoloration of teeth and enamel hypoplasia are permanent.

Hypersensitivity reactions are rare. Morbilliform rashes, urticaria, fixed drug eruptions, exfoliative dermatitis, cheilosis, glossitis, pruritus and vaginitis are described. Angioedema, anaphylaxis and pseudotumor cerebri have been reported.

Drug interactions

The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking tetracyclines.

Storage

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

Doxycycline

Group: antimicrobial agent

Capsule or tablet 100mg (as hyclate)

General information

Doxycycline is derived from and closely related to oxytetracycline, and has an identical spectrum of activity. It differs from the tetracyclines in that it is more extensively absorbed and more lipid-soluble, and it possesses a longer serum half-life that is independent of the patient's renal status.

Clinical information

Uses

Short-term prophylaxis of multiple-drug-resistant falciparum malaria. Because of limited experience, doxycycline should be used for prophylaxis only by persons who cannot tolerate mefloquine or who visit areas where mefloquine is no longer effective.

Dosage and administration

Adults: 100mg daily for up to 8 weeks.

Children over 8 years: 1.5mg/kg daily for up to 8 weeks.

Prophylaxis should be started 1 day before exposure and continued for 4 weeks after the last risk of exposure.

Contraindications

- Known hypersensitivity.
- Age under 8 years, since skeletal deposition can result in retardation of bone growth, hypoplasia of dental enamel and permanent brown discoloration of teeth.
- Pregnancy.

Precautions

Oesophageal ulceration may be averted if the patient sits or stands up for a few minutes while the tablets are swallowed, and if they are always washed down immediately with a glass of water.

Other symptoms of gastrointestinal irritability can be reduced if doxycycline is taken with a meal, but milk products must be avoided since they reduce absorption.

Use in pregnancy

Doxycycline is generally contraindicated in pregnancy. It impairs skeletal calcification in the fetus and can result in abnormal osteogenesis and hypoplasia of dental enamel.

Adverse effects

Gastrointestinal irritation is common and phototoxic reactions and increased vulnerability to sunburn have been reported.

Transient depression of bone growth is largely reversible, but discoloration of teeth and enamel hypoplasia are permanent.

Drug interactions

The action of oral anticoagulants may be potentiated. Severe renal failure has been reported in patients who have received a halogenated anaesthetic agent while taking doxycycline.

Storage

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

Proguanil

Group: antimalarial agent

Tablet 100 mg of proguanil hydrochloride

General information

Proguanil is a synthetic biguanide derivative of pyrimidine that is highly active against the pre-erythrocytic intrahepatic forms of *P. falciparum*. Its effect on the primary intrahepatic forms of other species is less well documented. There is evidence that it may be effective against *P. vivax* only immediately after the initial infection. It has no activity on the latent intrahepatic forms (hypnozoites) of *P. vivax* and *P. ovale*. It also has some blood schizontocidal activity, but this effect is slow and has no established clinical application.

Foci in which *P. falciparum* is resistant to proguanil and related compounds occur everywhere that malaria is endemic and particularly where it has previously been employed in mass prophylaxis.

Absorption from the gastrointestinal tract is rapid and peak concentrations are attained in the plasma about 4 hours after administration. It has a plasma half-life of 12–16 hours and is excreted in the urine and faeces both unchanged and as its active metabolite, cycloguanil.

Clinical information

Uses

- Prophylaxis for pregnant women and non-immune individuals at risk of exposure.
- Together with chloroquine, for short-term prophylaxis in travellers to areas with a low prevalence of chloroquine-resistant *P. falciparum*.

Dosage and administration

Adults including pregnant women: 200 mg daily.

Children:

- <1 year: 25 mg daily
- 1–4 years: 50 mg daily
- 5–8 years: 100 mg daily
- 9–14 years: 150 mg daily.

The recommended treatment schedule must be started 1 day before exposure and be sustained until after delivery in the case of pregnant women and for 4 weeks after the last risk of exposure in the case of non-immune individuals. This is sufficient to ensure elimination of *P. falciparum* and *P. malariae*, but not of *P. vivax* and *P. ovale*, whose residual hepatic forms often survive for long periods.

Contraindications and precautions

Proguanil should not be used in areas with known resistance to either proguanil or pyrimethamine since cross-resistance readily occurs.

The dose of proguanil should be reduced in patients with renal impairment (100 mg daily if creatinine clearance is 20–60 ml/minute).

Use in pregnancy

There is no evidence that proguanil is harmful in prophylactic doses during pregnancy. Because of the vulnerability of pregnant women to falciparum malaria, it should be used at full prophylactic dosage wherever the disease is prevalent and likely to be responsive to proguanil, if chloroquine is not available or is unlikely to be effective.

Adverse effects

Occasionally, patients develop mouth ulcers during treatment but, at the recommended prophylactic dosage, proguanil is generally well tolerated.

Overdosage

Gross overdosage gives rise to ab-

dominal pain, vomiting, diarrhoea and haematuria. No specific antidote exists and symptoms should be treated as they arise.

Storage

Tablets should be stored in well-closed containers.

Artemether

Group: antimalarial agent

Oily solution for injection 80mg in 1-ml ampoule

General information

Artemether is a lipid-soluble methyl ether of dihydroartemisinin which has very rapid schizontocidal activity against blood forms of *P. falciparum* and *P. vivax*. After intramuscular administration, peak plasma concentrations are attained within about 6 hours.

Artemether has been reported to clear fever in severe falciparum malaria within 30–84 hours.

to tolerate oral medication or for a maximum of 7 days.

Precautions

Artemether should be used for the treatment of severe falciparum malaria only where there is evidence that the antimalarial efficacy of quinine is declining.

For children, since the injected volumes will be small, it is advisable to use a 1-ml syringe to ensure that the correct dose is given.

Clinical information**Uses**

- Treatment of slide-confirmed severe falciparum malaria in areas where there is evidence that quinine is ineffective. Radical cure should then be effected with a full dose of an effective oral antimalarial such as mefloquine.

Dosage and administration

Adults and children over 6 months: 3.2mg/kg as a loading dose by intramuscular injection, followed by 1.6mg/kg daily until the patient is able

Use in pregnancy

Little experience has been gained with the use of this drug in pregnancy but it should not be withheld if it is considered life-saving to the mother.

Adverse effects

Neurotoxicity has been observed in animal studies but not in humans.

Cardiotoxicity has been observed following administration of high doses of artemether.

Storage

The oily preparation should be stored in tightly closed containers, protected from light.

Artesunate

Group: antimalarial agent

Tablet 50mg (artesunate)

Powder for injection 60mg of anhydrous artesunate in 1-ml ampoule + 5% sodium bicarbonate in 0.6-ml ampoule

General information

Artesunate is a water-soluble hemisuccinate derivative of artemisinin. It is unstable in neutral solution and the injectable formulation must be prepared immediately before use in 5% (w/v) sodium bicarbonate solution to produce the salt sodium artesunate. After parenteral administration, it is rapidly hydrolysed to the active metabolite dihydroartemisinin. The oral formulation is probably hydrolysed completely before entering the systemic circulation.

Artesunate has been reported to clear fever in patients with severe falciparum malaria 16–25 hours after parenteral administration.

Clinical information

Uses

- Orally: treatment of uncomplicated falciparum malaria in areas where there is evidence of chloroquine, pyrimethamine/sulfadoxine, mefloquine and quinine resistance. It should always be administered together with mefloquine in full therapeutic dose.
- Parenterally: treatment of severe falciparum malaria in areas where there is evidence of quinine resistance. Radical cure is then effected with a full course of an effective oral antimalarial.

Dosage and administration

Oral administration

Adults and children over 6 months: 5 mg/kg orally on the first day followed by 2.5 mg/kg on the second and third days in combination with mefloquine (15 mg/kg) in a single dose on the second day. In a few areas, a higher dose (25 mg/kg) of mefloquine may be required for a cure to be obtained.

Parenteral administration

The powder for injection should be reconstituted with 5% sodium bicarbonate and diluted in an equal volume of physiological saline or 5% (w/v) glucose. It should be administered immediately by either intravenous or intramuscular injection.

A loading dose of 2 mg/kg should be followed by 1 mg/kg after 4 hours and 24 hours. Thereafter a dose of 1 mg/kg should be given daily until the patient is able to tolerate oral artesunate or for a maximum of 7 days.

Contraindications

Oral artesunate should not be used during the first trimester of pregnancy.

Precautions

Parenteral artesunate should be used for the treatment of severe falciparum malaria only where there is evidence that the antimalarial efficacy of quinine is declining.

The powder for injection is difficult to dissolve and care should be taken to ensure that it is completely dissolved before parenteral administration. It

should always be used immediately following reconstitution. If the solution is cloudy or a precipitate is present, the parenteral preparation should be discarded.

Use in pregnancy

Little experience has been gained with the use of this drug in pregnancy but the parenteral preparation should not be withheld if it is considered life-saving to the mother.

Adverse effects

Drug-induced fever can occur.

Neurotoxicity has been observed in animal studies but not in humans. In view of the uncertainty about toxic effects, caution should be exercised when more than one 3-day treatment is given.

Cardiotoxicity has been observed following administration of high doses.

Storage

Tablets and powder for injection should be stored in tightly closed containers, protected from light.

Artemisinin

Group: antimalarial agent

Capsule 250mg

General information

Artemisinin is a potent and rapidly acting blood schizontocide. It is a sesquiterpene lactone isolated from the herb *Artemisia annua*. It is less potent than its derivatives and therefore must be given in higher dosage.

Clinical information

Uses

Treatment of uncomplicated falciparum malaria in areas where there is evidence that chloroquine, pyrimethamine/sulfadoxine, mefloquine and quinine are ineffective. It should always be administered together with mefloquine in full therapeutic dose.

Dosage and administration

Adults and children: 25mg/kg on the first day followed by 12.5mg/kg on the

second and third days in combination with mefloquine (15mg/kg) in a single dose on the second day. In some areas, a higher dose (25mg/kg) of mefloquine may be required for a cure to be obtained.

Contraindications

- Pregnancy during the first trimester.

Precautions

Artemisinin should be used for the treatment of severe falciparum malaria only where there is evidence that the antimalarial efficacy of quinine is declining.

Use in pregnancy

Little experience has been gained with the use of this drug in pregnancy but it may be used after the first trimester.

Adverse effects

Drug-induced fever may occur.

Artemisinin (continued)

Neurotoxicity has been observed in animal studies but not in humans. In view of the uncertainty about toxic effects, caution should be exercised

when more than one 3-day treatment is given.

Storage

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

Most protozoan infections causing diarrhoea are due either to amoebiasis or to giardiasis. However, cysts and oocysts of other protozoa are occasionally found in the faeces of patients with persistent diarrhoea.

Balantidiasis

Balantidium coli is highly prevalent worldwide in many animals, and notably in pigs, but it rarely causes disease in humans. Microscopic cysts shed in faeces are transmitted to humans in contaminated food and water. When ingested they transform into trophozoites within the large intestine. Most cases are asymptomatic but extensive necrotic ulceration can occur, resulting in fulminating dysentery and fatal intestinal perforation.

Control

Transmission is reduced wherever living standards are raised and particularly by the installation of piped water.

Treatment

- Tetracycline (500 mg four times daily for 10 days) is rapidly curative. Less consistent results have been obtained with 5-nitroimidazoles such as metronidazole.

Sarcocystosis

Sarcocystis hominis (*Isospora hominis*) and *S. suihominis* are highly prevalent in cattle and pigs in many regions. A transient mild gastrointestinal disturbance occurs when cysts are eaten in undercooked meat. Sometimes these become invasive and become embedded in the intestinal mucosa and in skeletal muscle, but only rarely do they cause diarrhoea or muscle pain.

Control

The parasite is killed by thoroughly cooking or by deep-freezing affected meat.

Treatment

Treatment is rarely necessary because the intestinal infection is usually self-limiting and, within the muscles, infection is generally asymptomatic.

***Isospora belli* infection**

Isospora belli is specific to humans. Although rare, it is widely distributed, particularly in tropical and subtropical climates. Oocysts excreted in the faeces may be ingested, causing diarrhoea, abdominal pain and loss of weight. Most infections are self-limiting but occasionally, and particularly in immunocompromised patients, they may persist for many months and give rise to malabsorption.

Treatment

Patients excreting oocysts in the faeces should be treated with sulfamethoxazole/trimethoprim (800 mg + 160 mg four times daily for 10 days), which is reported to be curative.

***Dientamoeba fragilis* infection**

Dientamoeba fragilis, which occurs worldwide and may be a cause of intermittent diarrhoea and abdominal pain, can be transmitted by *Enterobius vermicularis*.

Treatment

Treatment with diloxanide or another luminal amoebicide is justified only when symptoms occur.

***Entamoeba polecki* infection**

Entamoeba polecki occurs worldwide, but symptomatic infection in humans is rare. It has been implicated in cases of diarrhoea and abdominal pain, particularly in Papua New Guinea. Transmission probably results from transfer of cysts excreted by pigs or monkeys.

Treatment

A combination of diloxanide and metronidazole, as recommended for the treatment of *E. histolytica* infections, is claimed to be curative.

Cryptosporidiosis

Cryptosporidium spp are widely distributed in animals in tropical regions, and notably in calves. Oocysts shed in the faeces are transmitted to humans in contaminated food and water. They are an important cause of acute diarrhoea in children and in the terminal phases of acquired immunodeficiency syndrome (AIDS). No specific treatment exists.

***Blastocystis hominis* infection**

Blastocystis hominis, which is often associated with *Entamoeba histolytica*, may itself cause abdominal pain, anorexia and diarrhoea in heavy infections. If warranted, treatment with metronidazole 2g daily for 5 days is effective.

Pneumocystosis

Pneumocystis carinii, which has been classified both as a protozoan parasite and a fungus, is of low pathogenicity and rarely produces signs of infection in otherwise healthy persons. However, it is a frequent cause of opportunistic infection in patients who are immunocompromised, debilitated or malnourished. *P. carinii* pneumonia (pneumocystosis) is the most frequent immediate cause of death in patients with acquired immunodeficiency syndrome (AIDS).

The parasite is probably transmitted by direct contact from person to person. After migrating down the respiratory tract the organisms multiply in small discrete foci — many of which become cystic — in the alveolar septal walls of the lungs. Untreated, the infection develops into a diffuse interstitial pneumonia characterized by cough and dyspnoea, and ultimately by respiratory failure and death. It may either develop insidiously over several weeks or become overwhelming in a matter of days.

Treatment

Most cases in immunocompetent patients respond to sulfamethoxazole/trimethoprim given orally in high daily dosages for 2–3 weeks. Patients who are intolerant of, or unresponsive to, this treatment may benefit from pentamidine. Immunocompromised patients may require intravenous therapy.¹ Both pentamidine and sulfamethoxazole/trimethoprim are associated with a particularly high incidence of toxic effects in patients with AIDS. Sulfamethoxazole/trimethoprim is also associated with suppression of bone-marrow activity.

When no improvement is evident after 4–8 days of treatment with either pentamidine or sulfamethoxazole/trimethoprim, it is justifiable either to switch to the other drug or even to

¹ See also WHO model prescribing information: drugs used in sexually transmitted diseases and HIV infection. Geneva, World Health Organization 1995.

administer both concurrently. Additional candidate drugs are currently under assessment. Limited, but promising, experience has recently been gained with eflornithine, a trypanosomicide that inhibits ornithine metabolism, and trimetrexate, a lipid-soluble analogue of methotrexate, which is a potent inhibitor of *P. carinii* dihydrofolate reductase.

The first few days of antimicrobial treatment are critical, particularly in patients with AIDS, since the destruction of many dead parasites exacerbates the pre-existing inflammatory process and aggravates hypoxia. However, mortality can be substantially reduced if a corticosteroid — either oral prednisolone or, when necessary, intravenous methylprednisolone — is administered as soon as antimicrobial therapy is started to patients with an arterial oxygen tension of less than 70 mmHg (9.33 kPa) (see page 61). Oral prednisolone at the recommended dose has not been found to increase the vulnerability of AIDS patients to other opportunistic infections, with the possible exception of candidiasis and herpes simplex.

Prophylaxis and suppression of infection

Hitherto, drugs used to suppress the infection have been either unacceptably toxic or only marginally effective. Zidovudine has been claimed to reduce the frequency of relapse, but its effect is rarely sustained for more than a few months. Sulfamethoxazole/trimethoprim has been claimed to suppress infection in patients with AIDS presenting as Kaposi sarcoma, but adverse effects are often troublesome. Many patients are unable to tolerate the treatment, and zidovudine cannot be used concomitantly since it potentiates the risk of bone-marrow depression. Pyrimethamine/sulfadoxine has also been used but, again, severe toxicity and treatment failures have been reported. Pentamidine has been used intravenously since 1985 to treat clinically evident infections, but it is too toxic when administered by this route for preventive purposes. However, with the development of an aerosol formulation of pentamidine, many of the systemic toxic effects associated with the use of this drug are no longer observed and monthly treatment has been shown to reduce the risk of reinfection substantially. Unfortunately, widespread use of the aerosol formulation of pentamidine has been accompanied by

a rise in extrapulmonary *P. carinii* infection. More recently, concern has been expressed that resistance to antimicrobial agents may be emerging in *P. carinii* isolates or that they may be developing virulence factors that enable them to cause disease in the elderly and other vulnerable populations.

Sulfamethoxazole/trimethoprim

Group: antimicrobial agent

Tablet 100 mg of sulfamethoxazole + 20 mg of trimethoprim, 400 mg + 80 mg, 800 mg + 160 mg

Concentrate for intravenous infusion 400 mg + 80 mg in 5-ml ampoule

Oral suspension 200 mg + 40 mg in 5 ml

General information

The two components of this combination product have a similar anti-protozoal spectrum. They operate synergistically because they independently inhibit different steps in the enzymic synthesis of tetrahydrofolic acid, an essential metabolic process in susceptible protozoa.

Trimethoprim is absorbed more rapidly, is more widely distributed in tissues, and enters the cerebrospinal fluid more rapidly than sulfamethoxazole. Both compounds are moderately bound to plasma proteins, and each is excreted largely unchanged in the urine at a rate that gives a plasma half-life of about 12 hours.

Clinical information

Uses

Treatment of *Pneumocystis carinii* pneumonia and suppression of infection in immunocompromised patients.

Dosage and administration

All dosages are suitable for both adults and children.

Treatment

Oral administration:

Sulfamethoxazole 100 mg/kg + trimethoprim 20 mg/kg daily in two to four divided doses for 14–21 days.

Intravenous infusion:

Severely ill patients should receive

sulfamethoxazole 75 mg/kg + trimethoprim 15 mg/kg daily in four intravenous infusions, each administered in a 5% glucose solution in water over 60 minutes.

Oral dosage forms should be substituted as soon as they can be ingested. Patients receiving intravenous infusions who do not improve in 4–8 days should be transferred to pentamidine.

Suppression

Sulfamethoxazole 25 mg/kg + trimethoprim 5 mg/kg in two divided doses on 3 consecutive days each week for as long as immunosuppression persists.

Contraindications

- Known hypersensitivity.
- Severe hepatic or renal dysfunction.

Precautions

Treatment should be suspended immediately should a rash, or any other manifestation of sulfonamide hypersensitivity occur.

Patients with an arterial oxygen tension of less than 70 mmHg (9.33 kPa) should receive a corticosteroid — either oral prednisolone or, when necessary, intravenous methylprednisolone — as soon as treatment is started. Oral prednisolone should be given at a dose of 40 mg twice daily for 5 days, followed by 40 mg daily for 5 days and then 20 mg daily for 10 days. Parenteral methylprednisolone should be administered at a dose of 30 mg twice daily for 5 days, followed by 30 mg daily for 5 days and then 15 mg daily for 10 days.

Sulfamethoxazole/trimethoprim (continued)

The risk of sulfonamide crystalluria is decreased by maintaining a urinary output of at least 1.5 litres daily. Whenever possible, periodic determination of plasma sulfonamide concentrations should be undertaken. Peak plasma concentrations should be maintained at about 40 µg/ml.

Patients must be advised to seek medical advice should they develop a sore throat or fever during treatment. This advice can be of greater value than routine monitoring of the white cell count.

Elderly patients may be more susceptible to severe adverse reactions, especially blood dyscrasias. Their treatment with sulfamethoxazole/trimethoprim should not be unnecessarily prolonged.

Patients deficient in folate may require supplementary calcium folinate to prevent megaloblastic anaemia.

Use in pregnancy

Because the disease is life-threatening, treatment should in no circumstance be delayed.

Adverse effects

Nausea, vomiting, glossitis and skin rashes are common.

Trimethoprim may induce a megaloblastic anaemia responsive to folic acid.

Sulfonamide-induced hypersensitivity reactions can be severe. They include life-threatening cutaneous reactions such as erythema multiforme (Stevens-Johnson syndrome) and toxic epidermal necrolysis.

Other reactions include granulocytopenia, agranulocytosis, aplastic anaemia, thrombocytopenic purpura and toxic hepatitis. Occasionally, haemolysis may occur in individuals deficient in glucose-6-phosphate dehydrogenase.

Patients with AIDS receiving high dosages of sulfamethoxazole/trimethoprim for *P. carinii* pneumonia are particularly prone to develop skin rashes, recurrent fever, neutropenia and thrombocytopenia and serum transaminase levels are likely to rise.

Drug interactions

Maintenance requirements for sulfonylureas and coumarin anticoagulants are often reduced as a result of their displacement from plasma proteins by sulfamethoxazole.

Concomitant use of other inhibitors of folate metabolism (such as pyrimethamine, methotrexate and certain anti-convulsants) increases the risk of megaloblastic anaemia.

Overdosage

Symptoms of acute overdosage include vomiting, dizziness and confusion followed by visual disturbances, petechiae, purpura and jaundice. Crystalluria, haematuria and anuria may also occur.

Emesis or gastric lavage may be of value within a few hours of ingestion. Provided urinary output is satisfactory, a high fluid intake should be maintained. Haemodialysis may be of value in eliminating some of the drug. Otherwise, treatment is symptomatic and supportive.

Storage

Tablets, suspension and concentrate for infusion should be stored, protected from light, in well-closed containers.

Pentamidine

Group: antiprotozoal agent

Powder for injection 200 mg, 300 mg of pentamidine isetionate

Powder for inhalation 300 mg of pentamidine isetionate

General information

A diamidine compound with anti-protozoal activity. It is administered parenterally since it is unreliably absorbed from the gastrointestinal tract. It does not enter the cerebrospinal fluid. Detectable amounts remain in the liver and kidney for many months as a result of selective binding. Only a small fraction is excreted unchanged in the urine within 24 hours.

Clinical information

Uses

Treatment and prophylaxis of *Pneumocystis carinii* pneumonia in immunocompromised patients intolerant of — or unresponsive to — sulfamethoxazole/trimethoprim.

Dosage and administration

The powder should be reconstituted with "water for injection".

Treatment

Adults and children: 4 mg/kg administered daily for 14 days, either by slow intravenous infusion over at least 60 minutes or by deep intramuscular injection.

Patients with severe renal failure should receive these infusions on alternate days rather than daily.

Prophylaxis

Adults: 4 mg/kg administered by slow intravenous infusion at monthly intervals indefinitely or 300 mg by oral inhalation in a single dose every 4 weeks indefinitely.

Children: 4 mg/kg administered at monthly intervals indefinitely, either by slow intravenous infusion or by oral inhalation.

A suitable nebulizer should be used to provide a particle size of less than 5 µm.

Contraindications

- Known hypersensitivity.
- Severe renal impairment.

Precautions

Because of the risk of hypotension and syncope all patients should remain supine and under observation for at least 30 minutes after each injection.

When possible, blood pressure, full blood count and serum creatinine and blood glucose concentrations should be monitored daily.

In immunodeficient patients treatment may need to be interrupted or discontinued should acute deterioration of bone marrow, renal or pancreatic function occur.

Use in pregnancy

Use in pregnancy can induce abortion. However, because *P. carinii* pneumonia is potentially fatal, it should always be treated without delay.

Adverse effects

Mild nephrotoxicity occurs frequently and is usually completely reversible.

Acute hypotension and syncope are common after rapid i.v. infusion.

Pancreatic damage results initially in hypoglycaemia due to excessive insulin release. Subsequent insulin

Pentamidine (continued)


insufficiency and pancreatitis have been reported.

Other adverse effects include hypocalcaemia, gastrointestinal effects, confusion, hallucinations, cardiac dysrhythmias, local induration and, occasionally, sterile abscess. Rarely, thrombocyto-

penia, leukopenia, abnormal hepatic function tests and Stevens–Johnson syndrome have been reported.

Storage

Vials of dry powder should be stored below 30 °C. Dilute solutions should be stored between 2 and 8 °C and any unused portion should be discarded within 24 hours of preparation.



Toxoplasma gondii, a protozoan parasite that is distributed worldwide, is transmitted to humans in several ways. Cats, which constitute the most important reservoir, are the only animals to excrete oocysts in their faeces. These remain viable in moist soil for many months. When ingested, they release invasive forms that rapidly transform into tachyzoites, which multiply asexually in tissue macrophages. The intracellular tachyzoites then disseminate in the bloodstream and lymphatics to reach the brain, heart and lungs. As immunity develops, the tachyzoites form cystic aggregates (bradyzoites) predominantly in brain and muscle tissue; these remain latent, but subject to reactivation, throughout the life of the host. Other hosts include rodents, swine, cattle, sheep, goats, poultry and birds, all of which can harbour viable cysts in their muscles and brains for long periods of time. When infected meat from these animals is eaten raw or inadequately cooked, bradyzoites rapidly transform back into active and invasive tachyzoites.

In many communities most people have been infected by early adulthood. Those with competent immune systems do not develop clinically evident disease and primary infection is signalled, if at all, only by mild subacute lymph-node enlargement, often in the cervical region. If the immune system is compromised, however, infection holds serious implications:

- Primary infection in an immunodeficient patient may result in encephalitis, myocarditis or pneumonitis as a result of unconstrained multiplication of tachyzoites.
- Subsequent impairment of immunity in a previously infected person can lead to encephalitis or meningo-encephalitis if latent bradyzoites become reactivated. The acquired immunodeficiency syndrome (AIDS) has resulted in a marked increase in cases of toxoplasmic encephalitis, which often present as intracerebral space-occupying lesions.
- Congenital transmission is most unlikely to result from a previously established infection in a healthy immuno-

competent mother, but primary infection incurred early during pregnancy leaves the placenta and, subsequently, the rapidly developing embryo highly vulnerable to the disease until the protective maternal immunological mechanisms become responsive. If the mother is immunodeficient, a previously established latent infection may also result in congenital transmission. Many such cases, which result in spontaneous abortion, fetal death or severe congenital disease, must be anticipated as a consequence of the spread of AIDS. If signs of the disease are evident in liveborn infants, the sequelae are generally severe and include a potentially fatal syndrome in which hydrocephalus, hepatosplenomegaly with jaundice, mental retardation and chorioretinitis may occur. Congenital disease that becomes clinically apparent later in life is usually less severe, but it frequently results in ocular or neurological impairment. Globally, toxoplasma infection is the most common cause of chorioretinitis in early adult life.

Control

The risk of transmission can be greatly reduced if meat is adequately cooked and if scrupulous hygiene is maintained by persons most at risk. Vegetables and fruit should be washed carefully before they are eaten. Pregnant women should always wash their hands thoroughly before eating, and after contact with raw meat, cats or soil. All women of reproductive age should be aware of the risks associated with the disease.

In some countries pregnant women are screened serologically to detect seroconversion or a significant rise in the titre of toxoplasma-specific IgG antibodies, since treatment of the mother during pregnancy may prevent or lessen the severity of congenital infection in the child. However, because antibody titres need to be estimated on several occasions, this is a service that is too costly for most national authorities to provide.

Treatment

Pyrimethamine is normally used in combination with a sulfonamide (usually sulfadiazine) in patients who require treatment. Both compounds are inhibitors of folate metabolism and

they act synergistically to kill the tachyzoites. Calcium folinate, although expensive, should be administered concurrently every third day during treatment, whenever resources permit, to counteract the megaloblastic anaemia occasionally induced by these drugs. Patients should also remain well hydrated since sulfadiazine is poorly soluble in the urine. This combination is particularly effective because both of the drugs penetrate in therapeutically active concentrations into the cerebrospinal fluid. In patients sensitive to sulfonamides, pyrimethamine has been used alone to treat toxoplasmic encephalitis at dosages several times those otherwise recommended. The incidence of adverse effects, and in particular of bone-marrow suppression, at these dosages has not been assessed.

The more soluble sulfonamides appear to be less effective, but they are reported to be of value in the prophylactic management of immunocompromised patients. The commercially available combinations of pyrimethamine with sulfadoxine or sulfamethoxazole seem to be unsatisfactory in this context. The former has been associated with severe cases of Stevens-Johnson syndrome and toxic epidermal necrolysis while toxoplasmic encephalitis has been reported to develop in patients receiving the latter in prophylactic dosages.

Clindamycin, which is concentrated in the choroid, is claimed to be of value — at dosages ranging up to 2400 mg daily orally or 4800 mg daily intravenously — to treat chorioretinitis and, together with pyrimethamine, to protect immunocompromised patients who are sensitized to sulfonamides. It is not yet certain whether it is effective in the treatment of toxoplasmic encephalitis, but preliminary results of a controlled study show promise.

Primary toxoplasmosis in pregnant women

Because pyrimethamine has teratogenic potential, it cannot be used during the first trimester of pregnancy. Spiramycin, which is less toxic, may reduce the risk of congenital transmission during this period, but it does not readily penetrate into the cerebrospinal space and does not prevent the development of toxoplasmic encephalitis in immunodeficient mothers. It has been used in pregnancy at a dosage of 3 g daily in divided

doses throughout the first trimester. Where amniocentesis or ultrasound has provided evidence of placental or fetal infection, and therapeutic termination of pregnancy has not been acceptable, alternating 3-week courses of pyrimethamine/sulfadiazine and of spiramycin have been administered from the beginning of the second trimester until term.

Neonates with clinical, serological or parasitological evidence of infection

Pyrimethamine/sulfadiazine with calcium folinate is the most effective treatment. Dosage should be determined by the severity of the disease. All infants born to mothers known to have become infected during pregnancy should receive at least one 4-week course of pyrimethamine/sulfadiazine. Those with no signs of infection at birth, but who are subsequently shown to be infected either by serological testing or by clinical examination, require further courses of therapy. Alternating 4-week courses of pyrimethamine/sulfadiazine and 6-week courses of spiramycin (100 mg/kg daily) have been suggested as a means of reducing the risk of bone-marrow suppression. Severely infected infants with overt signs of the disease require urgent treatment, which needs to be maintained for at least the first year. During the first 6 months, pyrimethamine/sulfadiazine should be administered daily. Subsequently, alternating monthly courses of pyrimethamine/sulfadiazine and spiramycin have been used with success. Supplementary prednisolone 1–2 mg/kg daily should be added to suppress the inflammatory response when active chorioretinitis threatens sight or when the central nervous system is demonstrably involved.

Delayed chorioretinitis, carditis or encephalitis

Pyrimethamine/sulfadiazine and calcium folinate should be administered for at least one month. Recurrence is frequent and further courses may be given if the infection remains active. Clindamycin, which is concentrated in the choroid, is claimed to be comparably effective in chorioretinitis. Supplementary corticosteroids should be given when sight is threatened.

Active toxoplasmosis in immunodeficient patients

In immunodeficient patients treatment often has to be started empirically, sometimes on the basis of tomograms showing

multiple discrete lesions within the brain, typically arranged in ring formation. Pyrimethamine/sulfadiazine should be given to all HIV-infected patients, including pregnant women, suspected of having active toxoplasmosis. Both drugs penetrate into the cerebrospinal fluid in therapeutically active concentrations. Until recently, the recommended dosages were relatively low. However, recent experience of treating patients with AIDS indicates that higher dosages hold advantage, even though these patients are particularly vulnerable to adverse effects such as leukopenia, thrombocytopenia, fever and rash and are unlikely to tolerate daily treatment for more than 6 weeks. Intravenous clindamycin has been used in patients intolerant of sulfonamides but its value remains uncertain. Since relapse frequently occurs within 2 months, suppressive therapy with lower daily dosages should be continued indefinitely. Patients who are immunodeficient from other causes can often tolerate more prolonged initial courses of treatment, which should be continued ideally for several months but for at least several weeks after the disease has become quiescent.