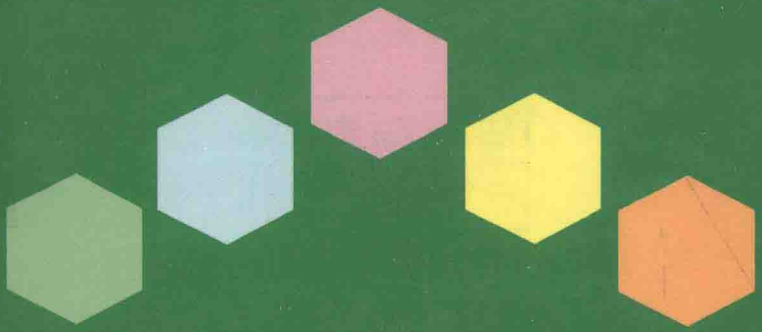
WHO MODEL PRESCRIBING INFORMATION

DRUGS USED IN PARASITIC DISEASES



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WHO Model Prescribing Information

Drugs used in Parasitic Diseases

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The World Health Organization is a specialized agency of the United Nations with primary responsibility for international health matters and public health. Through this organization, which was created in 1948, the health professions of some 165 countries exchange their knowledge and experience with the aim of making possible the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life.

By means of direct technical cooperation with its Member States, and by stimulating such cooperation among them, WHO promotes the development of comprehensive health services, the prevention and control of diseases, the improvement of environmental conditions, the development of health manpower, the coordination and development of biomedical and health services research, and the planning and implementation of health programmes.

These broad fields of endeavour encompass a wide variety of activities, such as developing systems of primary health care that reach the whole population of Member countries; promoting the health of mothers and children; combating malnutrition; controlling malaria and other communicable diseases including tuberculosis and leprosy; having achieved the eradication of smallpox, promoting mass immunization against a number of other preventable diseases; improving mental health; providing safe water supplies; and training health personnel of all categories.

Progress towards better health throughout the world also demands international cooperation in such matters as establishing international standards for biological substances, pesticides, and pharmaceuticals; formulating environmental health criteria; recommending international nonproprietary names for drugs; administering the International Health Regulations; revising the International Classification of Diseases, Injuries, and Causes of Death; and collecting and disseminating health statistical information.

Further information on many aspects of WHO's work is presented in the Organization's publications.

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Helminths

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 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 volume has been reviewed by internationally accredited experts, by all members of WHO's Expert Advisory Panel on Drug Evaluation and by selected members of the various WHO expert advisory panels on parasitic diseases. It has also been reviewed by certain nongovernmental 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.

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[1]WHO Technical Report Series, No. 770, 1988 (*The use of essential drugs*: third report of the WHO Expert Committee). (The fourth report of the WHO Expert Committee, containing the sixth Model List of Essential Drugs, is in preparation for publication in 1990.)

[2]Already published: *WHO model prescribing information: drugs used in anaesthesia.* Geneva, World Health Organization, 1989.

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. 1 & vol. 2 (Geneva, World Health Organization, 1979 & 1981) for definitions concerning containers for drugs.

Abbreviations used

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

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 clefamide, 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 7). 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 superinfection, 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 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
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 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 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 7.

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.

Use in pregnancy and lactation

Amoebic dysentery may run a fulminating course during late pregnancy and the puerperium. Treatment with metronid-

azole 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 leukopenia, 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 (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 antiamoebic 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 (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.

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

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.

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 inges-

tion. 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.