Drug Treatment of Disease

DRUG TREATMENT OF MALARIA

BY

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Life Cycle

The diagnosis of malaria rests on the recovery and identification of the parasites. Its treatment is governed by knowledge of the life cycle of the causative parasite. The recognized malaricidal drugs each act at certain points in the cycle of the parasite, not at all points. The diagram below sets out graphically the developmental cycles of the four malaria parasites of man: *Plasmodium falciparum*, causing malignant tertian (M.T.); *P. vivax*, causing benign tertian (B.T.); *P. ovale*, causing ovale tertian; and *P. malariae*, causing quartan (Q.) malaria. M.T. and B.T. are the most prevalent and ubiquitous.

There are two complete cycles and one partial cycle of development of the parasites in man. The first, or tissue phase, occurs in cells of the liver and probably of other organs in all four species during the incubation period of the disease. In B.T., ovale, and quartan malarials this tissue or extra-erythrocytic cycle persists in some form throughout the duration of the infection; it causes the relapses characteristic of these infections, as further infection of the red cells takes place from it. In the case of M.T. malaria alone the tissue phase is pre-erythrocytic only; it vanishes when the red-cell cycle is established; it cannot initiate relapse when the red-cell cycle has been destroyed. The asexual schizogony cycle in the red cells is solely responsible for the clinical manifestations of malaria in man. The gametogony cycle, arising from this blood cycle, ends with the formation of the pre-sexual gametocytes, which circulate in the blood merely to infect mosquitoes; they cause no inconvenience to their host.

Treatment of Clinical Attack

The arrest of acute uncomplicated malarial fever is readily achieved by the oral administration of one of the following drugs, which are listed in order of preference, with their dosage.

Chloroquine and Amodiaquine.—These are 4-aminoquinolines; the former is the more generally used. Chloroquine is sold in tablets of the diphosphate (250 mg. containing 150 mg. base), or sulphate (204 mg. containing 150 mg. base). An initial loading dose of 600 mg. base is followed after six hours by 300 mg. base, and thereafter by 300 mg. base on each of another two days.

Amodiaquine ("camoquin") is put up in tablets of the dihydrochloride dihydrate salt, each containing 200 mg. of the base. The loading dose is 600 mg. base; then 400 mg. base is given daily for two days.

Both drugs are absorbed rapidly, localized and slowly metabolized in the tissues, and excreted slowly. The toxicity of either in these doses is negligible and there are no contraindications to their use.

Mepacrine is an amino-acridine sold in tablets of the dihydrochloride dihydrate (100 mg. containing 78.5 mg. base). The dosage is 2 tablets (200 mg. salt) 4 or 5 times on the first day, followed by 1 tablet (100 mg. salt) thrice daily for another six days.

Mepacrine stains the skin yellow; it may cause colic and diarrhoea, nausea, and vomiting in those not habituated to it. In some cases mental changes, even maniacal, may attend its use. It is falling into disfavour for these reasons, and also because it increases the toxicity of the 8-aminoquinolines (see below) when given in association with them.

Quinine is sold as tablets of the sulphate, hydrochloride, bisulphate, or dihydrochloride. The first of these salts is virtually insoluble, the last very soluble. Absorption is rapid, so loading is not necessary. The dose is 10 gr. (650 mg.) of the sulphate, or other salt, thrice daily for five to seven days.

Quinine is bitter; it causes giddiness, tinnitus, and deafness in those not habituated to it. Graver symptoms may follow gross overdosage. Prescribing of it has fallen off owing to the introduction of the synthetic antimalarials, and to an exaggerated fear of its precipitating blackwater fever in cases of M.T. malaria. It is a safe and efficient drug for the control of fever due to any malaria parasite, provided that the patient has not previously been taking the drug irregularly.

In addition to these *proguanil* ("paludrine"), which is a biguanide, can be used as the monohydrochloride in tablets each containing 100 mg. (87 mg. base). Its action on the erythrocytic cycle is slow, as is the clinical response. It therefore is not satisfactory for clinical cure, but is reserved for prophylaxis, for which purpose it is excellent. *Proguanil* is devoid of toxicity in any advocated dosage. *Pyrimethamine* ("daraprim") resembles *proguanil* in most respects therapeutically. Inadequate dosage with either of these drugs results in a strain of parasites resistant to both of them.

Eradication of the Infection

In M.T. malaria thorough treatment of the acute attack, as already indicated, leads to destruction of the erythrocytic forms of the parasite and so eradication of

the infection. In the other types of malaria the continuing exo-erythrocytic cycle must be destroyed, as the drugs which control the clinical attack do not affect this cycle. The drugs which destroy the exo-erythrocytic cycle are given orally either concurrently with, or immediately after, treatment of the clinical attack. They are the following 8-amino-quinolines:

Pamaquine.—This is sold in tablets of the monohydrochloride (9 mg. containing 8 mg. base), or dihydrochloride (10 mg. containing 8 mg. base), or naphthoate (18 mg. containing 8 mg. base). The dosage is 8 to 10 mg. of the base thrice daily for ten days.

Primaquine.—One tablet of the diphosphate (13.5 mg. salt containing 7.5 mg. base) is given twice daily for ten days.

These two compounds may cause severe side-effects in the form of nausea, abdominal cramps, methaemoglobinæmia, cyanosis, and the passage of dark urine. Neither should be given in association with mepacrine, as this drug aggravates their toxicity. Patients taking them are best in hospital.

Treatment of Grave or Complicated Attack

M.T. malaria is so called because it may rapidly fulminate and give rise to grave complications commonly due to obstruction of small vessels, particularly in the brain, by parasitized red cells. In such cases speed and certainty in the control of the infection are imperative if life is to be saved. The advocated methods of oral treatment are entirely satisfactory if the patient is conscious and he can swallow and absorb the drugs. Often in pernicious malaria he is vomiting; he may be mentally deranged or comatose. Parenteral treatment is then necessary. The drugs used under such conditions in order of choice are:

Quinine Dihydrochloride.—7.5–10 gr. (500–650 mg.) of this freely soluble salt is given intravenously slowly (over 10–15 minutes), preferably well diluted in normal or glucose saline, and an intravenous saline drip is set up. It may be necessary to repeat the dose in the same manner after eight hours, and again after another eight hours, but this is rarely necessary. Oral treatment should replace the parenteral treatment at the earliest opportunity. After giving the initial intravenous quinine, treatment with chloroquine by mouth may be substituted. Quinine injected intramuscularly is prone to cause local necrosis.

Chloroquine Diphosphate.—200–400 mg. of the base is given intravenously in 500 ml. of normal or glucose saline over a period of one hour; another 200 mg. base is given after eight hours if occasion demands. Alternatively, 200–300 mg. base is given intramuscularly, and repeated after a similar interval if necessary. Intramuscular injection of chloroquine is quite effective and may be thought preferable to intravenous administration.

Mepacrine Dimethanesulphonate.—120 mg. in an ampoule is equivalent to 100 mg. of the dihydrochloride dihydrate. In default of one of the preceding two drugs, 200 to 300 mg. of this soluble salt may be given intramuscularly (not intravenously), and repeated at eight-hourly intervals if imperative. Mepacrine intramuscularly can give rise to considerable abscess formation, and it is better avoided in favour of quinine or chloroquine injections.

Semi-immune Persons

The indigenous inhabitants of countries where malaria is endemic, who have survived long-continued and repeated infection with the local strains of parasites, become tolerant of their infections and do not suffer the severe clinical manifestations to which new entrants are subject. When their infections do trouble them, one or two doses of any of the drugs effective against the erythrocytic infection will relieve them. Sterilization of their infections may be undesirable, because it results in a loss of their tolerance.

Prophylaxis and Suppression

Residents of non-malarious countries travelling to malaria-endemic areas should practise drug prophylaxis. There is no causal prophylactic which destroys the infective sporozoites injected by the mosquito. Proguanil and pyrimethamine, if taken regularly, will destroy the ensuing tissue or pre-erythrocytic stage of M.T. malaria, and so will sterilize this infection before it becomes erythrocytic. Neither they nor the other drugs available will do this in the case of B.T. and the other malarias. Any of the drugs acting on the erythrocytic cycle if taken consistently will prevent its development, or keep it at so low a level that it fails to cause clinical manifestations. This is therefore only suppression, or clinical prophylaxis. Proguanil and pyrimethamine are valuable for this purpose, especially in view of their specific effect on the very early M.T. infection. The drug selected must be taken with unfailing regularity. Those recommended and their doses are as follows:

Proguanil.—100 mg. daily, starting a week before arrival and continuing until 30 days after leaving. An allied preparation—lapudrine—has just been put on the market. It is said to be more persistent, so once-weekly dosage with this preparation is adequate. Alternatively, pyrimethamine may be given, 25 mg. once weekly. Strains of parasites can develop resistance to proguanil and pyrimethamine. Though rare and local, where such strains exist these drugs obviously should not be relied on.

Chloroquine.—300 mg. (base) once weekly, or *amodiaquine*, 400 mg. (base) once weekly.

Mepacrine.—100 mg. daily. Its yellow-staining tendency militates against its use.

Quinine should *not* be used as a chemoprophylactic if the other drugs are available; if they are not, the dose of quinine is 5–10 gr. (320–650 mg.) daily. Quinine is not an efficient chemoprophylactic or suppressive; where M.T. malaria is endemic, its use for this reason is associated with an increased incidence of blackwater fever.

Dosage Scales

The doses given for treatment are appropriate to normal adults weighing 9 to 12 stones (57–76 kg.). They can be adjusted by the usual age scales for children, with an increase on the generous side. The prophylactic, or suppressive, dosage for children can safely and with advantage be given at a higher level than the age scales would indicate. For heavy adults the therapeutic dosage should be rather higher and the prophylactic dosage should be double for those over 14 stones (88 kg.), as it can also be for normal persons subject to unusually heavy exposure to infection.