

CONTINUING MEDICAL EDUCATION

MANAGEMENT OF MALARIA

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Treatment of malaria, especially that of cerebral malaria has recently been extensively covered by several authors(1,2). We present here a brief account of the anti-malarials conventionally employed in the treatment of plasmodial infections in man, highlighting the present day problems and controversies in the management of malarial infection.

I. Management of Uncomplicated Malaria

Because of its rapid schizontocidal action and low toxicity, chloroquin remains the drug of choice for all cases of uncomplicated acute malaria, where drug resistance is not a problem (*Table I*). The initial loading dose of chloroquin is 10 mg base/kg given orally followed by 5 mg/kg repeated 6 hours later. The drug is contin-

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ued in the dose of 5 mg/kg/day for the next 2 days. A total adult dose of 900 mg of chloroquin (600 mg base) followed by 300 mg after 12 hours as followed at some centres may not be adequate in *P. falciparum* cases and, therefore, a total dose of 1500 mg chloroquin is recommended in all proved cases of *P. falciparum* malaria(3).

Individuals infected by *P. vivax*, *P. ovale*, and *P. malaria* tend to have frequent relapses as a result of tissue schizogony even after adequate schizontocidal drugs. These patients, therefore, require primaquin (8 aminoquinoline) for elimination of exoerythrocytic forms of parasites persisting in the liver (radical treatment). Primaquin, recommended in the dose of 0.3-0.5 mg/kg/day for 14 days for radical cure, is advised only for 5 days in the Indian programme due to logistic considerations and its toxicity.

The value of radical treatment in endemic areas where reinfection can not be prevented is debatable(3,4). However, radical cure in the Indogangetic planes may be given between December to March as the transmission of malaria is at its lowest ebb in Northern India during this time of the year(3). Though radical treatment as such is not required in *P. falciparum* malaria, a single dose of primaquin (0.9 mg/kg) is indicated for elimination of gametocytes and interruption of transmission. The drugs commonly used in treatment of malaria are summarized in *Table I*.

II. Management of Severe Malarial Infection

Severe infection, specially by *P. falciparum*

TABLE I—Drugs Commonly Employed in the Treatment of Malaria

Drugs/ Chemical Class	Dosage	Site of Action					
		Sporo- zoites	Pr. Exo- erythro- cytic phase	Asexual parasite	Erythrocytic Gameto- cyte	Latent exo- erythrocytic phase	Development of gametocytes in mosquito
1. Cincona <i>alkaloid</i> Quinine Oral	Loading dose 20 mg base/ kg followed by 10 mg base/kg × 8 hourly × 7-10 days	Nil	Nil	Fast	Acts on <i>P. vivax</i> & <i>P. malaria</i> • None of <i>P.</i> <i>falciparum</i>	Nil	Nil
IM IV	Not recommended 5-10 mg/kg, repeated 8 hourly; maximum 20 mg/kg in a day (Switch to oral therapy as soon as possible)						
2. 9 Amino- acridine- Mepacrine Oral (If other drugs not available)	I day 100-500 mg/day II day 100-300 mg/day followed by 50-150 mg/ day × 5 days (not for children < 6 months old)	Nil	Nil	Fast	as quinine	Nil	Nil
3. 4-Aminoquinoline							
(a) Chloroquin Oral	10 mg base/kg followed by 5 mg/kg and then 5 mg/kg × daily × 2 days.	Nil	Nil	Fast	as quinine	Nil	Nil
IM IV	5 mg/kg/dose } Switch to 5 mg/kg/dose } oral route as soon as possible						

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Drugs/ Chemical Class	Dosage	Site of Action					
		Sporo- zoites	Pr. Exo- erythro- cytic phase	Asexual parasite	Erythrocytic Gameto- cyte	Latent exo- erythro- cytic phase	Development of gametocytes in mosquito
(b) Amodiaquin Oral	20 mg/kg/dose (initial) 8-15 mg/kg/day (2-4 days)						
4. 8-Aminoquinoline Primaquin Oral (for radical treatment)	0.25 mg/kg/day × 2 weeks	Nil	Active (not used for Prophylaxis)	Active only in toxic doses	Active, specially good in <i>P. falciparum</i>	Highly active	Highly active
5. Biguanides Proguanil Oral	2-4 mg/kg/day × 5-10 days	Nil	Active spe- cially on <i>P. falciparum</i>	Relati- vely slow action	Nil	Nil	Highly active
6. Diamino pyrimidine pyrimethamine Oral	1.25 mg/kg of pyri- thamine combined with 20 mg/kg of sulphadoxin as a single dose	Nil	As above	Relatively slow action	Nil	Some action on <i>P. vivax</i>	Nil
7. Sulphon- amides Sulphadoxin Oral		Nil	Possible	Moderate action if given alone	Nil	Nil	Nil

parum is a medical emergency and calls for expert medical and nursing care. The child may present with cerebral malaria or with shock, cardiorespiratory failure, pulmonary edema, jaundice or severe anemia. Even in the absence of these immediate life threatening complications, children with high parasitemia (parasite load of more than 100,000/mm³ of blood, parasitization of more than 2% of red blood cells a RBC count of less than 2 million and a hematocrit of less than 30%) need very close observation preferably in an intensive care unit (ICU).

Children with severe malarial infection should receive either chloroquin or quinine parenterally, preferably the latter where there is a possibility of chloroquin resistance. However, the high incidence of dangerous and often lethal side effects of parental chloroquin in children(5,6) and the problem of increasing drug resistance has limited its use in severe malarial infection. Intravenous quinine diluted in dextrose saline is given slowly in a loading dose of 20 mg/kg followed by 10 mg/kg/day in three divided doses for 7 days(7). Intravenous quinine should, however, be replaced by oral administration as soon as possible. Thapa *et al.*(8) who employed IV quinine for either patients of cerebral malaria, switched over to tetracycline or metakelfin after 3 days of IV quinine.

Recently, quinidine(9) has been used as an alternative to quinine in the treatment of severe malaria. Phillips *et al.*(9) have advocated a loading dose of 15 mg/kg infused over half an hour. It is to be followed by a maintenance dose of 7.5 mg/kg (infused over four hours) repeated eight hourly. Controlled trials are needed to evaluate the efficacy and complications of quinidine in children.

Supportive Therapy

The value of general management in severe plasmodial infection can hardly be over emphasized. These patients should preferably be admitted in an ICU and attention given to appropriate fluid therapy and control of seizures. Careful monitoring of vital signs are imperative.

Dexamethasone, earlier used to treat cerebral edema, is no longer recommended in the treatment of cerebral malaria as it prolongs coma without significantly altering the mortality(10,11). Dextran was used in cases of cerebral malaria with the belief that it will improve the circulation in the small cerebral vessels by reducing the blood viscosity. The experience with dextran in Indian children has been disappointing. There are reports that dextran may cause severe anaphylactic reactions and bleeding(5).

Monitoring of Patients

Patients with severe falciparum malaria should be watched for complications both of disease as well as its treatment. The complications include.

1. *Hematological:* Severe anemia is an important feature in children with malarial infection. This requires slow transfusion of packed cells or whole blood. The hemoglobin concentration should be kept above 7 g/dl or 20% PCV. In severe parasitemia the role of exchange transfusion is being evaluated and the preliminary results are encouraging.

2. *Neurological:* Co-existent meningitis should be ruled out in all comatose patients as cerebral malaria may occasionally coexist with meningitis. There is an urgent need to carry out longitudinal studies in children with cerebral malaria to find out

the long term effects of this disease on scholastic, psychological and other finer aspects of intelligence.

3. *Gastrointestinal*: Children with severe falciparum malaria may present with massive gastrointestinal hemorrhage, vomiting, watery diarrhea and with shock. Correction of hypovolemia and replacement of blood loss with appropriate fluids is mandatory.

4. *Renal Complications*: Renal involvement in malaria is well documented and can develop with or without black water fever. Though Krishnan(12) could not document a single case of renal failure in his series, 8 of 70 children with *P. falciparum* malaria reported by Thapa *et al.*(13) had biochemical evidence of renal failure. Derangement in renal functions is, however, transient in most of the cases(14,15). It is secondary to heavy parasitemia without hemolysis or hemoglobinuria.

Treatment of acute renal failure includes replacement of fluid deficit and high doses of furosemide. Dopamine infusion may then be tried if these measures fail to increase urinary output. Ultimately one has to resort to peritoneal dialysis if urine output does not increase after dopamine infusion.

5. *Respiratory*: Acute pulmonary edema and aspiration pneumonia are important complications. Fluid overload should be avoided and central venous pressure should be maintained between 0-5 cm of water in such patients. Patients with pulmonary edema should be treated with oxygen, diuretics and vasodilators. Venesection may be tried in recalcitrant cases. Pneumonia should be treated with antimicrobials and Oxygen.

6. *Cardiovascular*: Circulatory collapse may be present at the beginning or during the course of disease. This commonly

results from other complications such as dehydration, gastric hemorrhage, pulmonary edema, sepsis and DIC. Treatment include correction of hypovolemia, vasopressors, and suitable antibiotics if associated with sepsis.

7. *Acidosis*: Lactic acidosis associated with hypoglycemia is an important complication of severe malaria. The role of bicarbonate for correction of acidosis is still controversial(1).

8. *Hypoglycemia*: Hypoglycemia is an important complication of severe falciparum malaria. This may also result during quinine therapy. This is treated by an intravenous infusion of glucose (25-50%) 1-2 ml/kg followed by 10% glucose infusion as maintenance.

9. *Sepsis*: Bacterial sepsis should be suspected in children with severe malaria who deteriorate after initial improvement. The treatment requires appropriate antibiotics.

Other Drugs used in the Treatment of Chloroquin Resistant Severe Malaria

1. *Mefloquin*: This drug is under extensive field trial in Africa and Far East and is not available for general use yet. In order to delay drug resistance against mefloquin, it is being used in Thailand in triple drug combination (Mefloquin, Sulphadoxin and Pyrimethamine). Because of lack of parental preparation, its use in severe malaria is limited.

2. *Qinghaosu*: This drug is a derivative from Chinese herbal preparation. Artemisinin (qinghaosu) is effective when given parenterally and holds a great promise as a future therapeutic agent for severe and complicated malaria(5).

3. *Sulphalene*: Metakelfin (Sulphalene + Pyrimethamine), Fansidar (Sulphado-

xine and Pyrimethamine), combinations of short acting sulphonamide and Trimethoprim and Tetracycline are generally used in chloroquin resistant malaria. They should not be used in the initial treatment of malaria. Indiscriminate use of these drugs will lead to multidrug resistant strains of *P. falciparum*. Quinine in combination with either tetracycline or metakelfin may also be used in the treatment of resistant falciparum malaria.

Some of the other drugs in different stages of development include Halofantrine and Empyroline.

Chemoprophylaxis

The role of chemoprophylaxis in the control of malaria is far from satisfactory. Thus long term use of antimalarials in highly endemic areas do not have a lasting effect either on endemicity or on the rate of transmission. Moreover, it may lead to development of drug resistant strains and lastly is, purely a logistic problem of covering the entire population at risk. Chemoprophylaxis as a malaria control measure, therefore, today aims only at reducing morbidity and mortality in "high risk groups" living in highly endemic areas. They include pregnant women, non immune visitors, migratory populations such as labour force, refugees in camps and army and police units. Routine chemoprophylaxis of children under 5 is not recommended as it is likely to interfere with the development of natural immunity(5). Drugs used for chemoprophylaxis are chloroquin and amodiaqui and combination of chloroquin and proguanil. Sulphadoxine/Pyrimethamine is no longer recommended for prophylaxis because of high incidence of toxicity. Studies are in progress to determine the value of triple combination of

drugs (Mefloquin, Sulphadoxine and Pyrimethamine) in prevention of malaria in regions where chloroquin resistance is common.

Malaria Vaccine

Vaccines have been successful in every animal model tested. The ultimate vaccine will probably contain antigens from different species and against different stages in the parasite's life cycle (sporozoite, asexual and gamete). Some of these undertrial vaccines are summarized below.

(a) Sporozoite Vaccines

This is the only vaccine successfully applied to humans. Vaccination, however, requires large number of X-ray attenuated sporozoites, limiting mass vaccination. If effective, a sporozoite based vaccine would eliminate the disease and transmission as well. However, if one sporozoite escapes the immune system, a virulent infection could occur. Further, they are species specific and produce short lived immunity not lasting for more than 3 months(16).

(b) Vaccines Against Liver Stages

They have a potential advantage over those against sporozoites in that the parasites are within these cells for at least 7 days. These forms have recently been cultured and it may be possible to identify malarial immunogens on the surface of these cells(17).

(c) Vaccines Against Asexual Stages

Blood stage vaccines (e.g., parasitized RBCs or cellular fractions) have been the most tested. The merozoite vaccines seem

to be the most promising as they consist of whole parasitized erythrocytes, merozoites or partially purified antigens. Research is on to identify antigens that can be synthesized. The two major points of attack are the antigens on the erythrocyte surface and the merozoite antigens(18).

(d) *Gamete Vaccines*

It would bring no protection to the recipient but can interrupt transmission(1).

Problems in Vaccine Development

Even if the immunogens were identified, they may not be effective without the use of adjuvants. Immunity to asexual erythrocytic infection with *P. falciparum* tends to be strain specific. Multiple strains exist within one area, each with unique antigens. Some malarial parasites can change their antigens in response to the host immune response. One last consideration will be the effectiveness of vaccines in young children and in semi-immune adults, many of whom may be infected at the time of vaccination. Work is on to develop a combination vaccine that will immunize against the sporozoite and merozoite stages(19).

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