E. V. Peiris Memorial Oration - 1994

The management of severe falciparum malaria

David A Warrell[1]

Journal of the Ceylon College of Physicians, 1995, **28**, 31-34

Dr E.V. Pieris, who died in 1992, is warmly remembered by the Sri Lankan medical community as a meticulous, conscientious and humane general physician and teacher, whose publications indicate the breadth of his interest, knowledge and experience. After qualifying in 1950 and working for a while in Britain, he was appointed a consultant physician at Colombo General Hospital in 1960. He resigned from the government service in 1972 but, fortunately for his many patients, he remained in practice as a physician working from his home.

Introduction

Malaria is one of the world's major killing diseases. More than 40% of the world's population, more than two billion people, are exposed to malaria where they live; 270 million a year are infected and a proportion, those who have not developed immunity, become sick with the infection[1]. The mortality could be anywhere between one and three million per year. The principles of management include early diagnosis and initiation of chemotherapy as early as possible and in particular the early use of appropriate antimalarial chemotherapy, the prevention of early detection and treatment of the many organ and tissue complications of this devastating protean infection[2].

Chemotherapy

One of the first lessons I learnt about severe falciparum malaria during our work in Thailand was that the earlier specific chemotherapy can be started the better was the prognosis[3]. The rapidity of the evolution of severe falciparum malaria is an important factor that must be borne in mind in the treatment of the disease. Dosage should, ideally, be calculated according to the patient's weight but we are still uncertain about the exact dose requirements at the extremes of weight — in very obese patients or those who are extremely wasted. Only the parenteral route is acceptable, but at the most peripheral levels of the health service it may in future be possible to use suppositories containing qinghaosu derivatives. Clearly, in a severe infection, it is insufficient just to prescribe the treatment. One must carefully monitor the response during the crucial hours and days after starting treatment, both clinically and with laboratory measurements. As soon as patients are fit to take drugs by mouth, they should be switched to oral treatment. Finally, one must always be aware of drug toxicity. Antimalarial drugs act at various stages of the life cycle of the malaria parasite in the mosquito vector and in the liver and circulating erythrocytes of the human host. In the case of severe falciparum malaria, only blood schizonticide drugs are employed, acting on the erythrocytic forms of the parasite. Probably the best, the most rapidly acting and the safest antimalarial drug ever invented by man was chloroquine. Chloroquine was first synthesized in 1934 and was first used as an antimalarial drug in the 1940s. It was one of the major elements of the global eradication campaign orchestrated by the World Health Organisation. However, resistance appeared in the early 1960s in *Plasmodium falciparum* and recently in *Plasmodium vivax* in New Guinea and adjacent areas of Indonesia. Today we are faced in many parts of the world with clinical and parasitological failure of chloroquine. This resistance must be taken seriously when treating a potentially life threatening disease such as severe falciparum malaria, but it is quite clear that chloroquine is still an effective treatment of uncomplicated falciparum malaria in some parts of the world such as areas of Sri Lanka and even northern Vietnam and parts of Africa such as the Denbia Plain in Ethiopia. Chloroquine resistance has now been reported in most parts of the distribution of *Plasmodium falciparum* and it is really only in the island of Hispaniola (Haiti and the Dominican Republic), in Central America northwest of the Panama Canal and in parts of West Africa and the Middle East that falciparum malaria remains sensitive to chloroquine. With the development of chloroquine resistance, a much older drug, quinine, came back into its own and is now widely used for the treatment of severe falciparum malaria. In Sri Lanka, there has been no convincing evidence of quinine resistance so far, although there is always the problem of potential quinine toxicity, especially hypoglycaemia resulting from insulin release[4]. Progressive quinine resistance may well develop in Sri Lanka, as in other Asian countries, with gradually increasing minimal inhibitory concentration of quinine for local strains of the parasite. Quinine is an unpleasant drug to take for prolonged courses of 7-10 days. Side effects include the syndrome

[1] *Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Headington, Oxford, UK.*

of cinchonism: dizziness, tinnitus, altered vision and nausea at quite low plasma concentrations. These symptoms have limited the use of quinine particularly in areas of emerging quinine resistance where courses longer than three or four days are necessary. A number of promising new antimalarial compounds and antimalarial strategies are being developed[5]. Atovaquone, a hydroxynaphthoquinone, has a unique mode of action, and is proving effective against multiresistant *P falciparum* infections provided it is combined with either proguanil or tetracycline to prevent rapid development of resistance. Desferrioxamine, an iron chelator, has demonstrated some antimalarial properties, as have some of the quinolone antibiotics. There are new anti-folate drugs and, to eliminate the persistent hepatic forms of *P vivax* and *P ovale*, a new 8-aminoquinolone[5]. Attempts have been made to reverse chloroquine resistance by the use of calcium channel blockers, tricyclics and anthistamines, so there is some prospect that eventually, chloroquine might be employed again in combination with a drug which will reverse the parasite's ability to leak chloroquine out of its vacuoles so avoiding the chemotherapeutic effect of this drug.

Early results from China, particularly from Hainan Island, suggested that the case fatality rate in cerebral malaria might be reduced from perhaps 15-20%, reported with quinine treatment in South East Asia and Malawi, to less than 10%. Artemisinin derivatives come from the sweet wormwood plant *(Artemisia annua)*[6]. The active metabolite of these compounds is dihydroartemisinin. A variety of artemisinin compounds are now being brought on to the market by western pharmaceutical companies collaborating with Chinese manufacturers (Table 1). Routes of administration of these derivatives include intramuscular injection (artemether and artesunate), intravenous injection (artesunate), tablets (artemisinin, artemether, artesunate) and suppositories (artemisinin). In China and Vietnam, artemisinin suppositories have proved effective in children with cerebral malaria and this route of administration has great advantages at the peripheral levels of the health service where it may be impossible to give injections and in particular intravenous infusions of antimalarial drugs. Clinical studies in China and elsewhere have demonstrated that artemisinin derivatives achieve a more rapid parasite and fever clearance than other antimalarial drugs (Table 2). Toxicity has been reassuringly rare in human patients and it is possible that the high recrudescence rates initially observed may have been the result of inadequate dosage. Unfortunately, assays of qinghaosu derivatives in blood and plasma have not produced results which are readily interpretable and so the pharmacokinetics and optimal regimens have not been derived. Two large randomised trials are at present in progress to compare the efficacy of intramuscular artemether with quinine in severe falciparum malaria: in adults in Vietnam, and in children in four African countries. Preliminary results from the latter study confirm the more rapid parasite and fever clearance achieved by artemether and, in Malawi, the duration of coma was less in the artemether-treated children. No advantage has been demonstrated in mortality or in the incidence of neurological sequelae. It may be that artemisinin derivatives will improve mortality only in areas where there is marked quinine resistance. In animal toxicity studies, artemisinin derivatives have proved neurotoxic and have produced histopathological damage in the brain stem in dogs and monkeys. These problems have not been encountered in any of the clinical studies.

Table 1. Artemisinin and its Derivatives

artemisinin (qinghaosu)	im/tablet/ suppository
artemether[1]	im/capsule/tablet
(arteether)	
artesunate	im/iv/capsule/tablet[2]
(artelinic acid)	
yingzhaosu (Ro42-1611)	
synthetic trioxanes, dioxanes	

[1] "Injectio Artemether" Kunming
"Paluther" Rhone-Poulenc Rorer Doma
"Artenam injection" Profarma

[2] "Artenam" Profarma
"Artesunate tablets" Guilin

Table 2. Artemisinin Derivatives: Clinical Efficacy

1 Rapid cure of *P falciparum* and *P vivax* (fever, parasite clearance, ? duration of coma)

2 ? reduced mortality in severe *P falciparum* infection

3 Negligible toxicity

4 High recrudescence/relapse rate after short/low dose regimens

5 Optimal dosage unknown (pharmacology difficult !) empirical: 5-7 day courses or combine with mefloquine/tetracycline

Ancillary treatment

Patients with severe falciparum malaria should be moved to the highest level of medical care available. In well equipped intensive care units, many complications, formerly lethal, can be effectively treated[7]. Recommended ancillary treatments include prophylaxis with phenobarbitone in cerebral malaria which, in Thai adults, reduced the incidence of generalised convulsions. Generali-

sed convulsions can result in persisting deterioration in neurological status and can provoke aspiration pneumonia. Acute renal failure can be treated with haemofiltration or haemo- or peritoneal-dialysis (Table 3). Acute pulmonary oedema, whether the result of fluid overload or of the ARDS type, formerly an almost invariably fatal complication in severe malaria, can now be treated with mechanical ventilation and the use of positive end expiratory pressure (Table 4). Severe anaemia often results from the high levels of parasitaemia and consequently extensive haemolysis encountered in severe falciparum malaria. However, the indications for blood transfusion (Table 5) have become much more stringent with the emergence of hepatitis viruses and retroviruses. In the case of "algid malaria" (severe malaria associated with circulatory failure) antimicrobial treatment is important to cover secondary gram negative rod septicaemia.

Table 3. Severe Falciparum Malaria: Acute Renal Failure

Indications for haemofiltration / dialysis

1 Hyperkalaemia
2 Uraemia
3 Metabolic acidosis
4 Pulmonary oedema

(? role of alkaline mannitol diuresis in haemoglobinuria / myoglobinuria)

Table 4. Severe Falciparum Malaria: Respiratory Failure

1 Acute pulmonary oedema (ARDS or overload)
2 Severe anaemia, metabolic acidosis, respiratory distress in African children
3 Respiratory arrhythmias / arrest (? brain stem compression)
4 2° pneumonias (aspiration)

Table 5. Severe Falciparum Malaria: Criteria for Blood Transfusion

1 Haematocrit low (< 15-20%) or rapidly falling
2 Haemorrhagic shock, anaemic heart failure
3 Bleeding, active or predicted (eg imminent parturition/ surgery)
4 Hyperparasitaemia
5 Failure to respond to oxygen and plasma expanders

Respiratory failure (Table 4) is increasingly recognised as a precipitant or accompaniment of death in severe falciparum malaria. Apart from acute pulmonary oedema, there is an emerging syndrome of severe anaemia (resulting perhaps from recrudescent attacks of malaria), metabolic acidosis and respiratory distress in African children (Marsh K, English M, personal communication). Respiratory arrhythmias suggest either focal ischaemia in the brain stem or perhaps brain stem compression.

Experimental ancillary treatments include exchange transfusion; chelating agents such as desferrioxamine which not only have an antimalarial activity but are also scavengers of free oxygen radicals which may be the common final pathway mediating tissue damage in severe malaria and other infections; anticytokine agents such as monoclonal antibodies directed against TNF α and dichloroacetate which can, in experimental animals, lower plasma lactic acid levels (Holloway P, Knox K, personal communication). Rejected ancillary treatments include adrenaline, heparin, corticosteroids, hyperimmune serum, cyclosporin A and oxpentifylline.

Exchange transfusion[8]

In patients with peripheral parasitaemias in excess of 10%, the prognosis is poor, and increasing numbers of physicians would now consider the use of exchange transfusion. The rationale of exchange transfusion is to reduce the circulating parasitaemia more rapidly than by optimal chemotherapy alone; to remove damaging toxins, cytokines and antigens; to restore the oxygen carrying capacity of the blood by replacing parasitised with non-parasitised erythrocytes; and to improve haemostatic function by providing clotting factors and platelets. Dangers of the procedure include shock (if cycles of exsanguination and transfusion are clumsily managed); introduction of known and unknown pathogens in large volumes of transfused blood from multiple donors; and infectious and other complications of intravascular catheters used in the procedure. In some of the published cases, ARDS has developed during the procedure. Exchange transfusion may dilute the circulating parasitised cells but may not affect the sequestered mass of parasitised cells thought to be responsible for pathophysiological effects. More than 70 cases of exchange transfusion have been reported in the literature, most of them successful, but there may well have been a reporting bias. No controlled comparative study has been carried out. There is increasing evidence that exchange transfusion can reduce the circulating parasitaemia more rapidly than chemotherapy alone, although with antimalarial drugs such as artemisinin derivatives, which clear parasitaemia more rapidly than quinine, this difference may not be important. Some of the patients improve clinically during the course of the exchange.

Severe malaria in pregnancy

Non-immune women, and primiparae even presumably "immune" women from endemic areas, suffer an increased incidence and risk of death from severe falciparum malaria especially during the third trimester of pregnancy. Early chemotherapy is essential. Physicians and obstetricians should not be discouraged from using quinine by its reputation as an abortifacient. In therapeutic doses, intravenous quinine has proved safe in pregnancy. If at all possible, uterine contractions and the fetal heart rate should be monitored before and after initiation of quinine treatment. Maternal temperature should be controlled as maternal fever can increase fetal distress. Pregnant women and their fetuses are particularly vulnerable to spontaneous and quinine-induced hypoglycaemia.

Raised intracranial pressure in African children with cerebral malaria

Observations, especially from the Kenya Medical Research Institute's Coastal Unit in Kilifi, have shown that opening pressures of cerebrospinal fluid at lumbar puncture are usually elevated in children with cerebral malaria. The pattern of neurological deterioration in some of these children suggested cerebral herniation[9]. CT scans during life show cerebral swelling[10], but post mortem findings so far have been inconclusive. However, in South East Asian adults, opening pressures were normal, there was little clinical suggestion of cerebral herniation and CT scans showed evidence of cerebral oedema only as an agonal phenomenon in a minority of severe cases[11]. The important issues, which cannot yet be answered finally are: should lumbar puncture remain the recommended rule in children with suspected cerebral malaria to exclude a treatable alternative diagnosis, especially bacterial meningoencephalitis?; should ICP-lowering agents such as mannitol or even dexamethasone be tried?; and should ICP be monitored?

Conclusion

Although the problem of severe falciparum malaria seems to be increasing in the world as a whole, relatively few cases have been seen in Sri Lanka over the last few years. However, the history of this island reminds us of the potential for large epidemics of falciparum malaria. It would be unwise to become complacent about this potentially devastating infection[12].

References

1. WHO Practical chemotherapy of malaria. Technical Report Series 805. 1990; WHO: Geneva.
2. Warrell DA, Molyneux ME, Beales PF (Eds). Severe and complicated malaria. Second edition. World Health Organisation Malaria Action Programme. *Trans Roy Soc Trop Med Hyg* 1990; **84**: Suppl.
3. Warrell DA, Looareesuwan S, Warrell MJ et al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. *NEJM* 1982; **306**(6): 313-9.
4. White NJ, Warrell DA, Chanthavanich P et al. Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *NEJM* 1983; **309**(2): 61-6.
5. Gilles HM, Warrell DA (Eds). Bruce-Chwatt's essential malariology. Edward Arnold: London. 1993 Third Edition.
6. Wellcome Trust Artemisia. Proceedings of a meeting convened by the Wellcome Trust on 25-27 April 1993. *Trans Roy Soc Trop Med Hyg* 1994; **88**: Suppl, S1 11-65.
7. Warrell DA, Phillips RE, Garrard CS. Intensive care unit management of severe malaria. *Clinical Intensive Care* 1991; 2(2): 86-96.
8. Looareesuwan S, Phillips RE, Karbwang J et al. *Plasmodium falciparum* hyperparasitaemia: use of exchange transfusion in seven patients and a review of the literature. *QJM* 1990; **75**: 471-481.
9. Newton CRJC, Kirkham F, Winstanley PA et al. Intracranial pressure in African children with cerebral malaria. *Lancet* 1991; **337**: 573-76.
10. Newton CRJC, Peshu N, Kendall B et al. Brain swelling and ischaemia in Kenyans with cerebral malaria. *Archives Dis Childhood* 1994; **70**: 281-7.
11. Warrell DA, Looareesuwan S, Phillips RE et al. Function of the blood-cerebrospinal fluid barrier in human cerebral malaria: rejection of the permeability hypothesis. *Am J Trop Med Hyg* 1986; **35**(5): 882-889.
12. Wickramasuriya GAW. Malaria and ankylostomiasis in the pregnant woman. Their more serious complications and sequelae. Oxford University Press: London, 1937.