EDITORIALS

1. CHLOROQUEINE-RESISTANT FALCIPARUM MALARIA:
   COMMENT

Chloroquine is the most widely used drug in the chemotherapy of malaria. Resistance to chloroquine by *P. falciparum* (the causative agent of *falciparum* malaria) was first reported by Young and Moore, in 1961. Since then resistant forms have been reported from East and Central Africa, the Far East, India, Central and South America.

Resistance to chloroquine by *P. falciparum* may take one of several forms. In the first type of Resistance (RI), clearance of asexual parasites from the blood occurs within 7 days after chloroquine treatment, but there is recrudescence within 28 days and this may be early or delayed. In the second type of resistance, there is marked reduction of asexual parasites in the blood but such parasites are never cleared completely from the blood, following chloroquine treatment. This type is referred to as RII resistance.

In RIII resistance, the level of parasitemia remains high despite chloroquine treatment. This type of resistance is seen in areas where resistance is widespread and of long duration. In all cases of suspected resistance, reduced sensitivity must be distinguished from actual resistance to chloroquine. In the former instance, the individual may be relieved of malaria symptoms following treatment with the normal dose of chloroquine for a slightly longer period (up to 7 days). Also re-infection must be excluded.

Strain selection to resistant forms may occur due to inadequate treatment. By this it is implied that exposure of strains of *P. falciparum* to subtherapeutic levels of chloroquine in the blood (e.g., following undertreatment) may lead to selection of resistant strains of the parasite. Several factors are responsible for inadequate treatment of *falciparum* malaria: self medication by patient; patient non-compliance due to side effects of chloroquine: notably, vomiting, nausea, pruritus; and above all, inadequate treatment by Doctors.

Patient non-compliance due to side-effects of chloroquine perhaps need to be given more attention now than in the past if further development of resistant strains is to be minimised. To this end there is the need for research into alternative drugs that would produce cure but that have little of such side-effects. But apart from this, complacency in the past by both clinicians and clinical scientists that chloroquine is so effective that development of resistance to chloroquine is unlikely, accounts for the present situation.

Even though in Ghana, suspicion of chloroquine-resistant strains of *P. falciparum* existed since 1965, these suspicions were not substantiated. A critical assessment of both studies suggests that but for poor experimental protocol including errors in methodology and failure to follow up patients after chloroquine treatment, chloroquine-resistant strains of *P. falciparum* might have been demonstrated. However there was no work in this area from 1968 until 1986 when for the first time, in vivo resistance to chloroquine at the RII level was reported in a patient with sickle cell disease who had been on malaria prophylaxis with chloroquine.

In this particular report disappearance of parasitemia occurred only after treatment with co-trimoxazole. However, the fact that chloroquine in a dose 80 per cent greater than the recommended dose did not reduce the parasite count to any significant extent 48 hours after initiating chloroquine treatment, suggests that resistance may have been at the RIII level rather than the RII level reported by Neequaye.

The implication of Neequaye's report are far reaching. It is evident that research into malaria chemotherapy has to be intensified in the light of the
presence of chloroquine-resistant strains of *P. falciparum*. The use of co-trimoxazole in treatment of acute malaria episodes had been reported much earlier than 1986. It was claimed that co-trimoxazole is as effective as chloroquine in the treatment of acute episodes of malaria. However the dosage of cotrimoxazole used was different from that used by Neequaye. The place of cotrimoxazole in the treatment of *falciparum* malaria needs further investigation.

The article by Ofori-Adjei et al. that appears in this issue, on chloroquine-induced pruritus is relevant to the problem of chloroquine resistance. The findings of this paper indicate that as many as 34 per cent of the population studied complained of chloroquine-induced itching. Given this fact, it follows that the potential for development of resistant strains of *P. falciparum* is great since these patients are less likely to complete the usual course of chloroquine prescribed by their doctors. Dr. Ofori-Adjei and others, also in this issue, report of chloroquine-resistant malaria in semi-immune Ghanaian children.

The conclusions that can be derived from the evidence so far available are: Development of chloroquine resistant strains of *P. falciparum* must have taken place over a long period, dating back from the 1960’s. The potential for development of more resistant strains exists due to problems arising from the use of chloroquine in the treatment of malaria. There is therefore the need to intensify efforts at finding alternate chemotherapeutic regimes against malaria particularly in patients who are unlikely to comply with doctors’ prescription for the treatment of malaria with chloroquine. And finally, it must be cautioned that if efforts are not made to tackle rigorously the problem of chloroquine resistance, then the situation in Thailand where it is said that a majority of infections by *P. falciparum* are chloroquine-resistant, may soon arise in Ghana and perhaps West-Africa.

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References


2. CHLOROQUINE-RESISTANT FALCIPARUM MALARIA: AN EMERGING PROBLEM IN GHANA

The main objective in the control of malaria is the prevention of mortality and reduction of morbidity from malaria. To achieve this objective demands a reliable system that allows for prompt recognition or diagnosis and adequate treatment of cases. There
should also be a means of protecting groups that are particularly vulnerable to the infection.

In Ghana, as in practically all African countries south of the Sahara, chemotherapeutic measures are the mainstay of malaria control. The success of chemotherapy as a control tool has been threatened by the emergence of strains of *Plasmodium falciparum* resistant to the main antimalarial drug, chloroquine. First reported in Columbia, chloroquine resistant *P. falciparum* infection had been limited to South and Central America, Asia and the Western Pacific until 1978 when the first well-documented case from Africa was reported.\(^1\) Since then chloroquine resistance has been reported in both non-immunes and semi-immune individuals from East and Central Africa. There has also been a rather rapid spread westwards along West Africa.\(^2\)\(^-\)\(^6\) Most of these reports have been on individual cases and could be an indication of the existence of a mutant gene that is responsible for the expression of resistance to chloroquine.

Clinical resistance of *P. falciparum* was first reported in Ghana in 1986\(^3\) in a sickle cell disease patient. Before then there were no conclusive evidence of resistance of *P. falciparum* to chloroquine.\(^7\)\(^-\)\(^8\) Subsequently there has been an increasing number of complaints of suspected resistance from various parts of Ghana. In 1987 however, in vivo resistance of RI and RII were documented in three children at the Department of Child Health of the Korle Bu Teaching Hospital using the WHO 7-day standard test\(^9\) during a surveillance study by the Centre for Tropical Clinical Pharmacology and Therapeutics and Department of Child Health of the University of Ghana Medical School.\(^8\)

Drug pressure is the major factor responsible for the selection of resistance in malaria parasites and subcurative doses and self-medication contribute towards their selection. The practice of self-medication with chloroquine for febrile episodes in Ghana is common.\(^10\)\(^11\) In addition a survey of prescriptions for chloroquine in Korle Bu Teaching Hospital indicates a wide variety of treatment regimes most of which do not add up to the recommended total dose of 25mg/kg body weight.\(^12\) For example an intramuscular injection of 5ml of chloroquine, equivalent to 200mg of the base, is considered enough to cure malaria. These practices aid in the selection of resistant strains.

The definition of in vivo chloroquine resistance assumes the persistence or recurrence of asexual forms of the parasite despite curative treatment and also freedom from fresh infection during the period of observation. This makes the diagnosis of RI (late recurrence) a problem in the field. It has been the practice in practically all laboratories in Ghana to report on peripheral blood films for malaria parasites as malaria parasites present or absent without indicating whether they are asexual or sexual forms. The presence of sexual forms (gametocytes) does not denote infection. The validity of resistance could be ascertained by reporting specifically on the presence of sexual and asexual forms in blood films. Blood films may also reveal other evidence of malaria infection like the presence of malaria pigment in blood cells. However, resistance once it occurs exists in all developmental stages of the affected strain.

The storage and shelf life of the numerous brands of chloroquine available in the country is uncertain and may result in low amounts of the drug in the administered form resulting in subcurative doses being given and hence "apparent resistance."

For the effective management of chloroquine-resistance, good epidemiological data is needed and this requires proper diagnosis of the condition. Hence as much as possible, clinical
diagnosis should be supported by laboratory diagnosis and where the expertise exists quantitative counts of the parasite should be done especially if resistance is suspected in the area.

Curative doses of chloroquine must be given to all patients diagnosed as suffering from malaria. The recommended curative dose of chloroquine is a total of 25mg/kg body weight given orally as three consecutive daily single doses of 10mg/kg; 10mg/kg and 5mg/kg body weight or a single oral dose of 10mg/kg followed six hours later by 5mg/kg then two daily doses of 5mg/kg body weight. Parenteral chloroquine should be reserved for severely ill patients, those with complicated malaria and those in whom oral administration is not possible on account of, for example, persistent vomiting or altered sensorium. Because of the potential toxicity of unduly high initial blood levels of chloroquine when given intramuscularly, the subcutaneous route may be a safer alternative. In any case a lower dose of 3.5mg base/kg body weight given 8 hourly over 72 hrs, results in a total dose that is slightly more than adequate, but acceptable.

For severely ill patients requiring intravenous drug administration the recommended treatment schedule is 5mg of chloroquine base/kg body weight in 10ml/kg body weight of Normal saline or 5% Dextrose infused over 4 hours, 12 hourly to a total dose of 25mg base/kg.

As soon as the patient can swallow, parenteral chloroquine administration should be changed to oral to complete the total dose of 25mg base/kg body weight. Where resistance to chloroquine is suspected in an area, chloroquine may still be life-saving since it will cause a decrease in parasitaemia in RI and RII resistance.

There is the need for regular quality control checks on preparations of chloroquine available on the market to ensure optimum quality drugs.

Finally, a treatment strategy based on the Primary Health Care System and a system of referral is needed to guide health care personnel in dealing with febrile patients suspected of suffering from malaria. Second line drugs are now needed in the management of malaria in Ghana and Quinine primarily and sulfadoxine/pyrimethamine are worthy of consideration.

D. Ofori-Adjei

References

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