Malaria ‘breakthroughs’ and resistance to chloroquine in Africa

Case reports

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Summary

Four cases of Plasmodium falciparum malaria are presented. These cases are typical of chloroquine-resistant malaria, with their pattern of ‘breakthrough’ malaria despite chloroquine prophylaxis, absence of response to therapeutic doses of chloroquine and recrudescence of the malarial parasites.

These cases should alert physicians in other parts of the world, who may have to treat travellers from Central and West Africa, and particularly from the Ivory Coast, to the possibility that the malaria contracted in these areas may be chloroquine-resistant.

The most effective drug in these cases appears to be a combination of sulphadoxine and pyrimethamine.

Since 1965 reports of chloroquine-resistant malaria in Africa have awakened an interest in the subject. Drugs other than chloroquine may be life-saving, and the most effective drug appears to be a combination of sulphadoxine and pyrimethamine (Fansidar). A similar preparation is used in South America, where chloroquine resistance is well documented.

Taabo Hospital, a Kaiser International Hospital Project, is located 175 km north of Abidjan, Ivory Coast, in an isolated river forest area that is endemic or hyperendemic for malaria. The hospital project was designed to provide care for the expatriate and Black employees of a hydro-electric dam scheme and their families as well as the local indigent Black population. There were approximately 300 expatriates and their families moving in and out of the area, and an estimated 2 000 Black employees from Central and West Africa and their families lived adjacent to the expatriates. Ideal conditions thus existed in Taabo for the introduction of resistant strains of Plasmodium falciparum.

Malaria was the major health problem among the Blacks and expatriates in the Taabo area, and malaria ‘breakthroughs’ were widespread among expatriates on chloroquine. A standardized medical approach was used for the treatment of acute malaria in adults, with 1 000 mg chloroquine given immediately, 500 mg 6 hours later and 500 mg daily for 3 days. This was a total of 3 000

mg in 72 hours or 1.8 g of chloroquine base. Reduced doses based on age and weight were given to children under the age of 12. Between 40% and 60% of the patients failed to respond to chloroquine. In these cases adults were treated with quinine 600 mg 3 times daily in combination with tetracycline 500 mg 4 times daily for 7 days or with a combination of sulphadoxine 500 mg and pyrimethamine 25 mg in tablet form taken in a single dose of 3 tablets. Chloroquine failure in children was treated with smaller doses of these drugs. In the expatriates, when possible, thick and thin blood films stained by the Giemsa technique for identification of malaria parasites were examined before treatment and after treatment if the symptoms failed to subside in 12 - 48 hours. Repeat blood films in patients on therapeutic doses of chloroquine frequently failed to show a significant reduction in malaria parasite levels or a change in levels after 300 mg of chloroquine. These cases were not dose-related. Repeat doses of chloroquine, 3 000 mg over a 72-hour period, often failed to change parasite levels significantly in these cases. The response to quinine and tetracycline in combination was unpredictable, but it was generally effective. A more consistent therapeutic response occurred with the combination of sulphadoxine and pyrimethamine. In these cases the parasites almost invariably disappeared from the blood film in 8 - 24 hours. Clinical improvement was usually evident in 4 - 12 hours.

Many Black employees were reluctant to take chloroquine for antimalarial prophylaxis because they so frequently developed chloroquine dermatitis from previous heavy exposure to chloroquine. The Ivory Coast medical and nursing staff had little confidence in chloroquine as an effective antimalarial drug.

Drug resistance to chloroquine was seen in a significant percentage of hospitalized Black infants and children observed to have swallowed chloroquine or having received it by injection. The Haskins urine test was positive in many of these cases.

Case reports

Case 1

A 44-year-old White woman weighing 42.4 kg developed fever, headache, vertigo and pain about both eyes on 12 June 1978. She had lived in Taabo for 28 months and had no previous history of malaria; previously she had lived in Venezuela for 3 years, in Ghana for 2 years and in Australia for 3 years. A thick blood film revealed P. falciparum (150 parasites/mm²). She had taken a prophylactic dose of 300 mg chloroquine base weekly, beginning 2 weeks before arrival in the Ivory Coast. Her last prophylactic dose of chloroquine had been taken 2 days before the onset of symptoms. A therapeutic dose was prescribed of 1 000 mg chloroquine to be taken immediately, 500 mg 6 hours later and then 500 mg daily for 3 days (a total of 3 000 mg in 72 hours). She miscalculated the dosage and took 2 000 mg chloroquine immediately, 1 000 mg 6 hours later and 1 000 mg the following day, a total of 2.4 g base in 24 hours, with no improvement in symptoms. The next day her oral temperature was 39.5°C. A repeat blood film revealed a parasite count of
100/mm³. On the 4th and 5th day of symptoms she again took 1000 mg chloroquine each day, making a total of 6.0 g in 3 days. A daily Haskins urine test was positive. Headache, vertigo, pain about the eyes and fever (oral temperature 39°C) persisted. On 17 June the parasite count was 125/mm³. She was given 3 tablets, each containing 25 mg pyrimethamine and 500 mg sulphadoxine, in a single dose. Blood films were free of malaria parasites 48 hours later and she recovered. This was felt to be an RIII type resistance (based on WHO Scientific Group criteria) after the standard oral postprandial treatment for moderately acute malaria.

**Case 2**
A 7-year-old expatriate Nigerian mulatto boy weighing 38.6 kg had lived in the Ivory Coast for 4 years. On 3 January 1978 he developed a fever with cough and frontal headache. His oral temperature was 38.5°C. A blood film on 4 January revealed *P. falciparum* infection (125 parasites/mm³). He had been on a regular weekly dose of 150 g chloroquine base. He was given 300 mg chloroquine base immediately, 150 mg 6 hours later and 120 mg daily for 3 days. The symptoms persisted and on 7 January a repeat blood film revealed an increased count of asexual malarial parasites (150/mm³). The daily Haskins urine test was repeatedly positive. He was given quinine 325 mg 3 times daily for 3 days and erythromycin 250 mg 4 times daily for 7 days. The headache and fever subsided within 48 hours and he felt well. A repeat blood film on 10 January was negative. This case was felt to be an example of RIII type resistance.

**Case 3**
A 51-year-old expatriate White man weighing 68.5 kg had worked in Taabo for 30 months. He developed chills, a fever of 39°C, subsided in 72 hours. On 3 October he again developed a fever of 38.9°C with chills. A blood film and the urine test were again positive. He was given quinine 325 mg 3 times daily for 3 days and tetracycline 500 mg 4 times daily for 7 days. The blood smears 72 hours later were free of parasites, with no recurrence of malaria during the subsequent 6 months.

**Discussion**
Four cases of *P. falciparum* resistance to chloroquine, in 3 adults and 1 child, are presented. Although in 3 of these cases the response to quinine and tetracyclines was satisfactory, it was unpredictable. Malarial resistance in the same patient to both quinine and chloroquine has been reported. This lack of response to quinine was occasionally observed at Taabo, where injectable as well as oral quinine was used in both expatriates and local Blacks. The response to sulphadoxine and pyrimethamine was dramatic and predictable, as has been observed elsewhere.

The frequently observed 'breakthroughs', resistance to chloroquine and recrudescence were widespread. Nearly all cases of malaria seen were due to *P. falciparum*, although occasionally *P. malariae* infection occurred conjointly. Several cases of *P. ovale* malaria were identified, as confirmed by slides sent to the Communicable Disease Center, Atlanta, Georgia, USA.

It would seem that in case 4 the latent stage of the parasite was present in the liver. All factors likely to introduce a strain or strains of resistant *P. falciparum* malaria into Taabo were present: (i) the expatriate employees were transient construction workers, tradesmen and professionals, 80% of whom had worked in areas of the world continued to take prophylactic chloroquine throughout this period and the Haskins urine test was repeatedly positive. Because of weakness, weight loss and malaise he was hospitalized and, suspected of having RIII chloroquine resistance, he was given quinine 650 mg 3 times daily for 3 days and tetracycline 500 mg 4 times daily for 7 days. The blood smears 72 hours later were free of parasites, with no recurrence of malaria during the subsequent 6 months.
where \( P. falciparum \) malaria resistance to chloroquine is known to exist; (ii) one-third of the expatriate employees moved in and out of the Taabo area as phases of construction were completed; (iii) company executives and administrators involved with the project regularly travelled in and out of Taabo from parts of the world where chloroquine resistance exists; (iv) \( P. falciparum \) parasite counts above 100/mm\(^3\) were found in a blood smear from a company executive visiting Taabo; he had been in Taabo for 48 hours before developing symptoms and had spent the previous 3 weeks in south-east Asia; (v) one-fifth to one-third of the local Black employees and their families as well as the surrounding indigent population were continually moving in and out of the Taabo area from Central and West Africa, including Mali, Senegal, Chad, Upper Volta, Ghana, Togo, Benin and Nigeria as well as other areas. This produced an unstable community — an ideal situation for the introduction of resistant strains of \( P. falciparum \) malaria.  

Although ‘malaria breakthroughs’ despite chloroquine prophylaxis had occurred from the start of the project and the opening of the Taabo Hospital in 1976, it was not until the end of 1977 that the extent of the ‘breakthroughs’ and chloroquine resistance became apparent, even though the expatriate and Black populations were relatively constant in November and December 1977 (Figs 1 and 2).

The weather also played a role, with mosquito populations increasing during the end of the rainy season in November and December and the beginning of the dry season (Fig. 3).

REFERENCES

14. Ibid., p. 43.