LEADING ARTICLES:

FALCIPARUM MALARIA NOT SENSITIVE TO CHLOROQUINE EMERGES IN ACCRA IN 1987

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Summary

In late 1987, there was an increase in the numbers of children with severe malaria seen at the Korle Bu Teaching Hospital. Thirteen children with falciparum malaria suspected to be resistant to chloroquine were studied. Resistance at the RII level was demonstrated in 2, and at the RI level in one. RI resistance to amodiaquine in one child was also seen. The factors leading to antimalarial drug resistance are discussed.

Key words:
P. falciparum; Chloroquine resistance

Introduction

Since the 1950’s, chloroquine has remained the drug of choice for treatment of an attack of falciparum malaria in West Africa and has also been used for prophylaxis. Resistance of P. falciparum to chloroquine is now widespread in South East Asia, and South America. It occurred in East Africa in 1979, 1 and has recently spread to Angola 2 and Cameroon. 3 A case of resistance was reported from Ghana in 1986 4 and reports from Nigeria 5 and the Gambia 6 indicated recent reduced sensitivity to chloroquine. In 1987 the weather pattern in Ghana was unusual, and a very long dry season was followed by heavy late rains occurring in Accra between September and November. During and after the rains we have observed an increase of severe falciparum malaria in children in Accra. Admissions to the Children’s Emergency Ward of the Korle Bu Teaching Hospital usually averaging between 700 and 800 per month, rose by 50% to 1200 in October and November 1987, the increase being largely due to cases of severe malaria. Clinical observations suggested that the therapeutic response to chloroquine was different this year from that in previous years, in that parasitaemia was not clearing as expected. It was thought that this may be due to resistance to chloroquine, and the following study was instituted.

Materials and Methods

Between October 20, 1987 and December 22, 1987, 13 children with suspected chloroquine-resistant malaria admitted to the Children’s Block of the Korle Bu Teaching Hospital were studied. Children with a clinical diagnosis of malaria who were reported to have received a course of treatment with chloroquine but still had parasitaemia were studied. Only patients who were not dangerously ill were selected for study. Those who were seriously ill were treated with an alternative drug if the clinical state deteriorated. All patients were admitted to the ward for observation and supervised administration of chloroquine. Thin and thick blood smears were done for species identification and quantitative counts of trophozoites and gametocytes respectively before starting treatment with chloroquine, and then daily

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Until parasitaemia cleared. Parasites were counted in relation to white blood cells (WBC) and the count converted to parasites per microlitre of blood. Chloroquine was administered as follows: Initially 5mg/kg was given intramuscularly, followed by 5mg/kg orally after 6 hours, repeated 12 hours later and then daily for 2 days, aiming at a total of 25mg/kg.

Results

Of the 13 patients admitted with falciparum malaria suspected to be resistant to chloroquine, this was confirmed in 3 cases. Two had resistance of the RII type, and one of the RI type. In addition, in one patient whose treatment was changed to amodiaquine because she was very ill, RI resistance to amodiaquine (camoquine) was demonstrated.

Case 1: Was a one year old girl who had received chloroquine syrup 1 teaspoonful (5ml) twice a day for 5 days prescribed from an Accra Polyclinic before being referred to us. The history was thought to be reliable and she was said not to have vomited the medication. After the initial parasite count which was 27,600 per μl of blood, she was treated with chloroquine injection 5mg/kg, intramuscularly followed by 5mg/kg orally after 6 hours, repeated 12 hours later and then daily for 3 days. Medication was administered under supervision by the ward nurses and she did not vomit it. She did not receive a blood transfusion. She continued to have trophozoites although at a reduced count but by Day 10 the count was rising. She was then given amodiaquine syrup 10mg/kg start and 5mg/kg for 2 days and parasitaemia cleared.

Case 2: Was a six-month old boy whose elder sister was already admitted on our ward with malaria. He had a blood smear examined for malarial parasites because he was febrile. It was positive and he was given chloroquine syrup twice a day for 3 days in the ward by a reliable nurse to a total of 40mg/kg; that is more than the recommended dose. He did not vomit the syrup. Parasite counts were commenced on Day 4. The trophozoites were not cleared until Day 9 although he was clinically improved. This again is resistance at the RII level.

Case 3: Was a 7-year old female who had been admitted to our ward 16 days previously with malaria and severe anaemia. She was admitted and transfused. After the transfusion she received 50mg/kg of chloroquine over a period of 3 days; that is, twice the recommended dose. It was given by a reliable nurse and she did not vomit the medication. Parasitaemia cleared and she was discharged. She returned for follow-up 11 days later febrile, with a parasitaemia of 42,800 P. falciparum trophozoites per μl of blood and 80 P. falciparum gametocytes per μl of blood. She then received 25mg/kg of chloroquine over 3 days and parasitaemia cleared. This was most probably an early rerudescence, RI. However re-infection can not be excluded.

Case 4: Was an 8-year old girl who had received irregular medication with chloroquine before admission. She had received an injection of unknown dosage 4 days previously, and then 4 tablets (600mg base) 2 days before admission. Initial investigations showed numerous P. falciparum parasites in her blood. She received two tablets of chloroquine (300mg base) on admission and another two tablets 12 hours later. At this stage there were still numerous parasites seen in her blood and because she was very ill, chloroquine was discontinued. Oral amodiaquine 10mg/kg was given followed by 5mg/kg daily for 3 days. She was discharged on Day 5 when no trophozoites were present in the blood. Eight days later she became ill again with fever and vomiting and received medication at a private clinic with no improvement. When seen by us
2 days later she had *P. falciparum* parasitaemia of 27,000 trophozoites/µl of blood. She received another full course of amodiaquine with clinical improvement, but she still had parasitaemia on Day 4. Thirteen days later she again had fever and a trophozoite count of 2,500 µl of blood. She received a 3rd course of amodiaquine. Parasitaemia cleared and she remained well. This case demonstrates 2 recrudescences of malaria after being adequately treated with amodiaquine and shows resistance at the RI level.

Of the other 9 cases, 4 cleared their parasites with a course of chloroquine administered in hospital, 3 were discharged too early and had inadequate follow-up; in 2 cases medication was changed to amodiaquine because the patients were too ill to justify continuing the study. Parasitaemia cleared in these 2 on amodiaquine.

**Discussion**

Chloroquine, a 4 aminoquinolone, is a potent antimalarial drug, which is well absorbed and in fact oral administration is the preferred route in the absence of vomiting or severe illness. 7 It is faster acting and more potent than sulphadoxine/pyrimethamine combination (Fansidar), which can be used to treat a mild attack of malaria, and is safer and easier to administer than quinine, which is the only real alternative in a severe complicated attack. 8 In severe malaria, quinine has to be administered intravenously with cardiac monitoring. Quinhasu derivatives, which are effective in severe malaria, are only available so far in China. A newer drug, mefloquine, has been in use in South East Asia in severe malaria, but resistance has already emerged 9 and it is now used in combination with sulphadoxine/pyrimethamine. Possible primary resistance of *P. falciparum* to mefloquine has been reported from Nigeria, 9 and from East Africa. 10

Falciparum malaria is often fatal in non immune people without adequate treatment. A study done in 1978 showed that 40% of children and 7% of adults in an area of Accra were non immune, perhaps due to frequent chloroquine administration and infrequent attacks of malaria. 11 In hyperendemic rural areas natural immunity is lowest around the age of 1–3 years, and this is the age group most likely to die from cerebral malaria and anaemia. If chloroquine resistance becomes widespread in West Africa, this will represent a very serious problem, particularly in non-immunes, who will suffer increased mortality and morbidity. Semi-immune adults will also have increased morbidity with increased length of time to get over an attack of malaria and therefore reduced productivity at work. Resistance to the alternative drugs for treatment like amodiaquine, sulphadoxine/pyrimethamine and mefloquine has been shown to emerge relatively quickly when these are used extensively, and that means that quinine would again be the mainstay of treatment. In a severe attack, and a high percentage of attacks in non-immune children are severe, the administration of intravenous quinine would necessitate admission to a hospital with the requisite staff and equipment. This would greatly increase the work load of such hospitals and overload resources that are already stretched to the limit. In the rural areas, such facilities do not exist near enough to the patients’ places of residence.

Drug pressure is one major contributory factor to the emergence of resistant strains of *P. falciparum*. Inadequate or incorrect dosage results in the parasites being exposed to suboptimal levels of the drug in the blood and aids in the selection of resistant strains. This situation is occurring with chloroquine at the present time in Ghana 12 for several reasons. Firstly some doctors do not prescribe a full 3-day course of treatment with at least 25mg/kg body weight, on
the grounds that the patient is semi-immune. Others give daily injections of chloroquine, usually of 5mg/kg body weight. This latter practice will lead to subtherapeutic blood levels and is not supported by recent pharmacokinetic data. Secondly, patients may not complete the course of chloroquine treatment because of local trust in the power of injections. Self-medication for febrile episodes with chloroquine is common and usually involves subcurative doses. This practice also aids in the selection of resistant strains.

What are the answers to this impending problem? There is no easy answer. Firstly doctors, nurses and the general public should realise that malaria is a very dangerous disease, and each doctor should take general steps to prevent the transmission, by cleaning up breeding sites for the mosquito, and by the use of mosquito netting and insecticides. Mass antimalarial chemoprophylaxis is expensive and may contribute to the selection of resistant strains. Their use may also be associated with fatal side-effects. Stevens Johnson syndrome is a serious side effect of sulphadoxine/pyrimethamine and agranulocytosis has been reported with the use of amodiaquine and sulphadoxine/pyrimethamine.

*P. falciparum* resistance to chloroquine is relative. At the R1 level resistance to chloroquine may be overcome in many cases by increasing the oral dose, and by lengthening the course of treatment. This resulted in clearance of parasitaemia in some of our small group of patients. It is vitally important that health professionals and the public become aware of the curative dose of chloroquine: at least 25mg/kg. Chloroquine should not be indiscriminately used. A patient who does not have malaria, does not need chloroquine. This calls for better diagnosis and use of laboratory facilities. It should also be remembered that even when chloroquine is fully effective, a heavy parasitaemia takes several days to clear, and if the patient’s condition is not deteriorating, doctors should not panic and assume drug resistance. In many cases parasitaemia may be present up to the 4th day although most infections clear by 72 hours. The parasite count should however be reducing. If it is not and the patient’s condition is deteriorating alternative treatment may have to be used. In conclusion it is only by the methods outlined here, that is, by reducing the drug pressure, and by using adequate treatment schedules, that chloroquine has a chance of remaining a useful drug.

References


