ORIGINAL ARTICLE

Chloroquine Resistant Falciparum Malaria in Children

by

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Abstract

From March 1981 until August 1985, 79 children suffering from falciparum malaria were treated with chloroquine upon admission to the Department of Child Health, Medical School Sam Ratulangi University/Gunung Wenang General Hospital, Manado.

Twenty one out of 79 patients were within range of the criteria of resistance as established by WHO: Standard field test or 7 days test. Six (28.6%) out of 21 patients belonged to resistance II (R II) to chloroquine. The duration of fever in the 6 patients with R II to chloroquine was 2–7 days, with the average of 3.3 days. Patients with R II to chloroquine were treated with Fansidar, and all of them were cured.

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Introduction

Drug resistance in malaria has been defined as the "ability of the parasite strain to survive and/or to multiply despite the administration and absorption of drug given in doses equal to or higher than it is usually recommended but within the limits of tolerance of the subject" (WHO, 1973). In this paper the parasite strain was *Plasmodium falciparum* and the drug chloroquine.

Chloroquine, found by Andersag in 1943 (cited from Adhyatma, 1983), was started to be used in the treatment of malaria in 1946 and it successfully had reduced the use of quinine since the malaria eradication program was introduced in 1959. For 25 years chloroquine had successfully been used as the main drug for the treatment and suppression of malaria, until alternative drugs for the treatment of chloroquine resistance were found (Adhyatma, 1983).

The first report on chloroquine resistant *Plasmodium falciparum* was in 1960, from Columbia, South America (Bruce-Chwatt, 1981) and after that there were reports from Thailand in 1961, Malaysia in 1962, Cambodia and Laos in 1964, Vietnam in 1967, the Philippines in 1970, Burma in 1971, and Sabah in 1972 (WHO, 1973). From West Africa, report came from Kenya and Tanzania in 1978 (WHO, 1984).

From Indonesia the first report in 1973, of 3 cases of falciparum malaria resistant to chloroquine, came from Samarinda, East Kalimantan (Verdrager and Arwati, 1975) and the other cases according to clinical observations from Sulawesi (Clyde et al., 1976). From Jayapura, Irian Jaya, Verdrager et al. (1975) found 7 cases. Ebisawa et al. (1976) reported 2 cases from Irian Jaya, and 4 cases from Sangkulirang, East Kalimantan. By 1983 all provinces in Indonesia had reported the existence of such resistance including in North Sulawesi, from Bolaang Mongondow in 1982 and Sangir Talaud in 1983 (Adhyatma, 1984).

This study was made to investigate the possibility of this resistance in Manado and the surroundings of Minahasa.

Materials and Methods

From March 1981 until August 1985, 79 children suffering from falciparum malaria were treated with chloroquine base, based on the dose of 10 mg/kg body weight/day for three consecutive days starting upon admission to the Department of Child Health, Medical School Sam Ratulangi University/Gunung Wenang General Hospital, Manado.

Blood film for falciparum was examined every day for 8 consecutive days from day 1 (on admission) until day 8, with guidelines for interpretation as follows: Negative means no parasite (trofozoid) on 100 microscopic field sight; positive (+) means 1-10 trofozoids on 100 microscopic field sight; positive (+ +) means 11-100 trofozoids on 100 microscopic field sight; positive (+ + +) means 1-10 trofozoinds on 1 microscopic field sight; positive (+ + + +) means 11-100 trofozoids on 1 microscopic field sight.

This resistance test was performed on patients following the criteria: 12-145 months of age; only *Plasmodium falciparum* found in blood film examination; asexual parasite density on the first day minimally positive (+ + +) and maximally positive (+ + + +) with not more than 30 parasites on 1 microscopic field sight; the children were not in so bad clinical conditions and had a fair enough general condition; they should be free from chloroquine, quinine and tetracycline for 14 days and also free from sulphones, sulphodoxine/prymethamine 4 weeks before admission.

Results

Twenty one out of the 79 treated patients were within the criteria of resistance as established by WHO: Standard field test or 7 days test for determination of chloroquine resistance of the *Plasmodium falciparum*.

Six (28.6%) out of 21 patients were resistant II (R II) to chloroquine. The 21 patients consisted of 9 girls and 12 boys.

The duration of fever before treatment of the 6 R II patients was 5-28 days with an average of 13.7 days, while of the 15 patients who were sensitive/resistant I (S/R I) it was 1-30 days with an average of 7.8 days (Table 1).

Table 1 : *Duration of fever before treatment in chloroquine resistant patients*

Resistance	No. of patients	Duration of fever	Average
R I	6	5-28 days	13.7 days
S/R I	15	1-30 days	7.4 days

As for the habitat of patients it revealed that 16 lived in Minahasa outside Manado, 5 of them with R II, while 5 patients lived in Manado, 1 of them with R II (Table 2).

Table 2 : *The habitat of 21 patients suffering from falciparum malaria*

Residence	No. of patients	S/R I	R II
Outside Manado	16	11	5
Manado	5	4	1
Total	21	15	6

Of the 5 patients with R II from outside Manado, 2 patients were from Warembungan, 1 from Lemoh, 1 from Pineleng and 1 from Wusa village, while 1 patient from Manado city came from Perkamil.

The duration of fever in the hospital of the 15 patients who were S/R I was 0–4 days with the average of 1.4 days, while of the 6 patients with R II it was 2–7 days with the average of 3.3 days (Table 3).

Table 3 : *Duration of fever in hospital in chloroquine resistant patients*

Resistance	No. of patients	Duration of fever	Average
S/R I	15	0–4 days	1.4 days
R II	6	2–7 days	3.3 days

Discussion

In this study, 21 patients were within the criteria of resistance as established by WHO: Standard field test or 7 days test (cited from Adhyatma, 1984). In 6 (28.6%) of them the density of parasites was significantly decreased though *Plasmodium falciparum* was still found on the 8th day, indicating that it belonged to resistance II (R II) to chloroquine.

In 1967 a team of WHO experts on malaria treatment (cited from WHO, 1980; Adhyatma, 1984) grouped the degree of resistance of asexual parasites (*Plasmodium falciparum*) to schizontocidal drugs (chloroquine) as follows (Tabel4).

Table 4 : *Degree of resistance of Plasmodium falciparum to schizontocidal drugs*

Response	Recommended symbol	Evidence
Sensitivity	S	Clearance of asexual parasitemia within 7 days of initiation of treatment, without subsequent recrudescence.
Resistance I	R I	Clearance of asexual parasitemia as in sensitivity followed by recrudescence.
Resistance II	R II	Marked reduction of asexual parasitemia but no clearance.
Resistance III	R III	No marked reduction of asexual parasitemia.

The scheme of standard test and extended test can be seen as follows (WHO, 1973; Wernsdorfer and Kouznetsov, 1980):

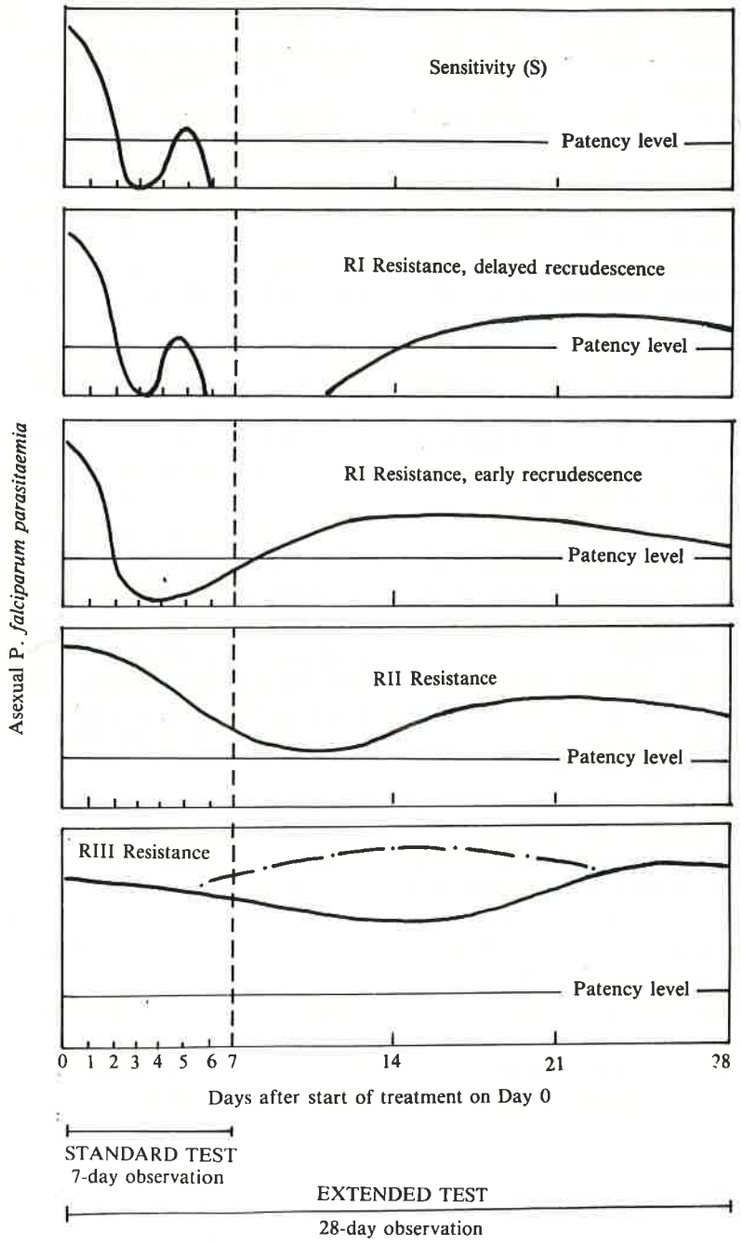

Fig 1. : *Scheme of standard and extended test for resistance of Plasmodium falciparum to schizontocidal drugs (Wernsdorfer and Kouznetsov, 1980)*

Resistance of *Plasmodium falciparum* to chloroquine has been reported by many countries, including Indonesia.

In Indonesia, Verdrager and Arwati (1974) reported 3 cases from Samarinda, East Kalimantan; Verdrager and Arwati (1975) reported 1 case from Balikpapan, East Kalimantan; Verdrager et al. (1975) reported 7 cases from Jayapura, Irian Jaya. Ebisawa et al. (1976) reported 6 (9.5%) out of 63 malaria cases, 4 of them from Sangkulirang, East Kalimantan and the other 2 from Irian Jaya; Verdrager et al. (1976) reported from Balikpapan that 3 (15%) out of 20 malaria cases were resistant, 2 of them R II and 1 R I. Pribadi et al. (1983) reported 14 (63.6%) out of 22 malaria cases were resistant, 6 from Lampung and South Sumatra, 1 from Prajurit Island in the Sunda Strait, 2 from Untung Jawa Island/Seribu Island in Jakarta bay, and 2 from East Timor. The authors found 6 (28.6%) to be resistance II to chloroquine, 1 from Manado and 5 from Minahasa outside Manado.

From Asean countries Harinasuta et al. (1965) reported 40 (95.2%) out of 42 cases in Thailand; Smrkovski et al. (1982) from Mindoro, the Philippines reported 4 (44.4%) out of 9 cases. Mashaal (1986) reported a research in Thailand (1972–1975) on 11 cases, all of them were resistant cases (100%). WHO (1984) reported that in Thailand, on the average more than 85% of all cases were resistant to chloroquine; in Malaysia, Ponnampalam (1984) reported that more than 70% were resistant to chloroquine, based on his research in 1980.

The duration of fever before hospitalization (Table 1) in patients with R II was 13.7 days on the average, while those with S/R I was 7.4 days.

Adhyatma (1983) stated that in the treatment of falciparum malaria with the standard dose of chloroquine, unless the fever disappears in 24 hours, resistance to chloroquine should be suspected.

Swai et al. (1983) stated that if the fever continued for more than 48 hours after starting chloroquine treatment, resistance to chloroquine must be suspected.

In this study (Table 3) we can see that the duration of fever in R II was 2–7 days with the average of 3.3 days, while in S/R I it was 0–4 days with the average of 1.4 days. That means a number of the S/R I patients were R I, while in this study (with 7 days test) we were not able to separate sensitive and resistance I.

In a WHO meeting in Kuala Lumpur in 1981 (cited from Adhyatma, 1983) experts suggested to change the chloroquine to an alternative drug if in the use of chloroquine for treatment of or as a prophylactic for malaria, the percentage of *Plasmodium falciparum* resistance to chloroquine in an area was as follows: 5% in in-vivo test (R I and or R II/R III) or 1% R II and or R III, or 5% in in-vitro test.

In this study 6 patients with R II to chloroquine were treated with Fansidar with doses of 20 mg sulphadoxine or 1 mg pyrimethamine/kg body weight/day for 2 consecutive days, and all of them were cured. To combat the gametocytes, primaquine base 1/2 mg/kg body weight was also given in a single dose to these patients.

The authors consider this study as a rough study, with a wide deviation/error. To narrow the deviation/error, it would be better to make the extended test 28 days combined with an in-vitro test (macro or even micro).

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