

Chloroquine-Resistant *Plasmodium falciparum* in the Iwahig Area of Palawan Island, the Philippines

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ABSTRACT: A field examination on the chloroquine sensitivity of *Plasmodium falciparum* in acute infections was carried out in the Iwahig Penal Colony of Palawan Island, the Philippines, during the periods of September, 1971, to January, 1972, and of January to February, 1973. The standard chloroquine dosage to subject patients was 25 mg base/kg body-weight over 3 days and the follow-up examination for the parasites was made for 17 days (Day 0 to Day 16) on the subjects who were kept admitted in the medical units established in the survey area. Results obtained were as follows: (1) The recrudescence of asexual parasites was found in 44 (RI in 40, RII in 4) of 90 subjects examined (48.9%). Five RI recrudescences were additionally detected among 18 subjects who were examined during the shortened follow-up period. (2) To the 44 recrudescing patients, 35 mg chloroquine base/kg over 3 days was administered and 6 (RI in 5, RII in 1) of them exhibited recrudescence again. (3) In relation to the RI recrudescence cases to the standard dosage of chloroquine, the detection of the earliest recrudescence was done on Day 6 and the number of the detection of recrudescences on each day thereafter tended to increase as days passed until the end of the follow-up period. (4) In the number of days until the initial clearance of asexual parasitaemia from the beginning day of chloroquine administration, no significant difference was found between two groups of the RI recrudescence cases and the cured cases. (5) From the results obtained, it could be concluded that the falciparum strains resistant to chloroquine had distributed in the area of the Iwahig Penal Colony.

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Since the 4-aminoquinoline derivatives were known as drugs with the most effective schizontocidal activity to malaria parasites, they have been broadly used everywhere in the endemic areas of malaria for treatment as well as prophylaxis of the disease. As a matter of fact, the malaria control measure in many areas has achieved a great success by use of this series of antimalarials. On the other hand, the development of the malaria strains resistant to the drugs has given us a serious problem. Up to the present time, a clear evidence for the existence of the 4-aminoquinoline-resistant falciparum strains has been presented from many areas in Southeast Asia, and Central and South Americas.

In the Philippines, the resistant strains of *Plasmodium falciparum* to chloroquine or amodiaquine were found in patients with acute infection in the Iwahig Penal Colony of Palawan Island by Ramos *et al.* (1971); at Montalban, a town near Manila, by Clyde *et al.* (1971); and in the Manila area by Shute *et al.* (1973).

This field survey was undertaken to examine on the response of *P. falciparum* to chloroquine in prisoners (colonists) with acute falciparum infection in the Iwahig Penal Colony. This colony has been well known as a malarious area in the country (Alves *et al.*, 1968; Ramos *et al.*, 1971; Cabrera *et al.*, 1972; Nakabayashi *et al.*, 1973). As the result, many recrudescence cases to the standard dosage of chloroquine were found, which could be an evidence for the possible existence of the chloroquine-resistant falciparum strains in the area.

This survey was conducted in cooperation with members of the Malaria Eradication Service, Department of Health, Republic of the Philippines.

SURVEY TIME

The survey was done in 2 separate times: the 1st time was the period from September, 1971, to January, 1972, and the 2nd, January and February, 1973.

SURVEY AREA AND SUBJECTS

The Iwahig Penal Colony selected as an area for this survey was located in the central part of Palawan Island and had approximately 4,000 colonists in an area of about 390 square kilometers. Palawan Island is slender in form and mountainous, and is situated between the South China Sea and the Sulu Sea in the southwesternmost portion of the Philippines. This island has been designated by the Philippine Government as a priority area for malaria control, because it has shown the highest malaria endemicity as compared with other areas of the country. Geographical and climatic circumstances of the island were previously stated by Nakabayashi *et al.* (1973).

Colonists were each assigned to a section or unit in one of the following 5 subcolonies; Central, Montible, Santa Lucia, Bagong Buhay, and Inagawan, and engaged in a forced labor. The 1st time of survey was conducted at the Iwahig General Hospital estab-

lished in the Central Subcolony. All the doors and windows of a big room of the hospital were covered with nylon meshes to prevent mosquitoes from flying into the room and all subjects were received in the room throughout the examination period. Acute falciparum patients to be examined were selected from outpatients who were mostly sent from the Central and Montible Subcolonies. In the 2nd, patients with acute falciparum infection among colonists of the Montible Subcolony were confined in the Montible Infirmary for the examination of chloroquine sensitivity.

All patients desirous of consultation were applied to a blood examination for malaria parasites. The relative count of asexual parasites enumerated in a thick blood-film with a microscope (magnification: $\times 500$) was signed according to the following code:

+	: 1-10 parasites per 100 fields	++	: 11-100 parasites per 100 fields
+++	: 1-10 parasites per field	++++	: more than 10 parasites per field

When necessary to ask the accurate expression of a parasite count with a thick film, it was calculated by the way as described below:

First: the number of parasites was counted in each field against the number of leukocytes in such a field until the leukocyte number reached 100 to 500.

Second: the number of parasites was calculated in relation to the number of leukocytes per cubic millimeter which was counted beforehand with a haemocytometer.

Among falciparum patients, those having the clinically serious or parasitologically intense symptoms, and showing such a small parasite count as one parasite in some dozen fields of a thick film, were excluded from the subjects. Regardless the grade of parasitaemia, patients who complained of frequent vomiting were excepted, as a rule.

The subject patients thus finally selected had the parasite count over the higher grade of the "one plus", and most of them showed 38°C or higher fever and also complained of chills or the chill sensation at the time of the blood examination. The number of subjects was 90 in total; 34 in the 1st time of survey and 56 in the 2nd. They all were males of more than 18 years.

CHLOROQUINE DOSAGE AND METHOD OF EXAMINATION

Chloroquine diphosphate tablets used in this survey were Rezochin (Bayer) and Aralen (Park Davis) which contained 150 mg base per tablet. The dosage to a patient was 25 mg chloroquine base per kilogram body-weight over 3 days according to the standard regimen which had been recommended by the WHO Expert Committee (1968) for a field test on the chloroquine sensitivity of *P. falciparum* in patients. The daily doses were decided to be 10 mg/kg first and 5 mg/kg 6 hours later on the first day (Day 0), and 5 mg/kg on the second (Day 1) and the third (Day 2) respectively, based on the descriptions by Covell *et al.* (1955) and WHO (1967), and on the authors' previous experience.

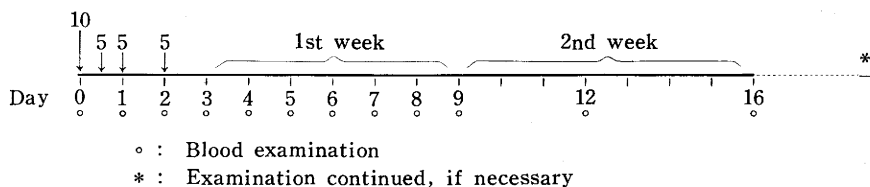
The follow-up examination for malaria parasites was made every day for 10 days

(Day 0 to Day 9), and on Day 12 and Day 16. The total follow-up period was shortened to 17 days (Day 0 to Day 16) due to various circumstances, though a 28-day examination was recommended for this test by WHO (1968) and others. The urine test for chloroquine estimation was failed to be done. The schematic procedure of the examination was indicated in Fig. 1. Recrudescing patients to 25 mg chloroquine/kg administration were treated again with 35 mg/kg dosage for the purpose of examining on the response of the parasites to the increased dosage of the drug. For an expression of the recrudescence of parasitaemia, 3 signs of RI, RII, and RIII were employed in accordance with a description by the WHO Expert Committee (1968). The daily doses of chloroquine by body-weights were shown in Table 1.

Table 1. Daily doses of chloroquine by body weights

B. W. (kg)	40 35~44	50 45~54	60 55~64	70 65~74
(25 mg chloroquine base/kg B. W.)				
Day 0	450 mg	450	600	600
	(6 hours)			
	150	300	300	450
Day 1	225	300	300	300
Day 2	225	225	300	450
Total	1,050	1,275	1,500	1,800
(35 mg chloroquine base/kg B. W.)				
Day 0	450 mg	600	750	900
	(6 hours)			
	300	450	450	450
Day 1	375	450	450	600
Day 2	300	300	450	450
Total	1,425	1,800	2,100	2,400

Chloroquine (mg/kg)



Chloroquine diphosphate : Rezochin or Aralen, 150 mg base/tablet

Dosage : 25 mg chloroquine base/kg body-weight over 3 days

Fig. 1. Method of examination on chloroquine sensitivity of falciparum parasites in patients with acute infection.

RESULTS

1. Recrudescence of parasitaemia

A. Results in the 1st time of survey

Of 34 patients administered orally the standard dosage (25 mg/kg) of chloroquine over 3 days, 11 exhibited recrudescence during the follow-up period. Thus the recrudescence rate was 32.4%. Other 23 were cured parasitologically as well as clinically without recrudescence. Of the 11 recrudescences, 10 were regarded as the RI type and the rest 1 the RII. One of the RI cases was detected on Day 6 in the first week after

the chloroquine treatment, other 7 in the second week (Day 10 to Day 16), and the remaining 1 on Day 20. The initial clearance of asexual parasitaemia was achieved in 2.8 ± 0.9 days (mean and 95% confidence limits) in the 10 RI cases (one who recrudesced on Day 20 was omitted) and in 2.4 ± 0.5 days in the 23 cured cases respectively. The 11 recrudescing patients were given 35 mg chloroquine/kg over 3 days and 2 of them showed the RI recrudescence to the increased dosage.

In this field survey, 46 vivax patients were found and treated with the standard dosage of chloroquine in combination with 15 mg primaquine base/day for 14 days. All of them were cured within several days, showing a rapid clearance of parasitaemia and had no recrudescence during the survey period.

The above-mentioned results were summarized in Table 2.

Table 2. Results of examination on chloroquine sensitivity of malaria parasites in patients to treatment with 25 mg or 35 mg chloroquine base/kg over 3 days

Chloroquine treatment	No. of subjects	Cured without recrudescs.		Recrudescences		
		No. (%)	Days*	No. (%)	Type	Days*
(At the Iwahig General Hospital, Sept., 1971, to Jan., 1972)						
Falciparum						
25 mg/kg	34	23(67.6)	2.4 ± 0.5	11(32.4)	{ RI : 10** RII : 1	2.8 ± 0.9
35 mg/kg	11***	9(81.8)	2.3 ± 0.9	2(18.2)	RI : 2	
Vivax						
25 mg/kg****	46	46(100.0)	1.8 ± 0.2	0		
(At the Montible Infirmary, January and February, 1973)						
Falciparum						
25 mg/kg	56	23(41.1)	2.8 ± 0.3	33(58.9)	{ RI : 30 RII : 3	2.8 ± 0.3
"Incomplete follow-up"						
35 mg/kg	33***	29		4	{ RI : 3 RII : 1	
25 mg/kg	18	13		5	RI : 5	

* : The number of days (mean and 95 % confidence limits) until the initial clearance of asexual parasitaemia

** : Including one who recrudesced on Day 20

*** : Recrudescing patients to 25 mg/kg of chloroquine

**** : Combined with 15 mg primaquine base/day for 14 days

B. Results in the 2nd time of survey

To each of 56 acute falciparum patients, 25 mg chloroquine/kg was administered over 3 days. The complete cure was observed in 23 patients but the recrudescence of asexual parasitaemia was found in other 33, so the recrudescence rate was as high as 58.9%. The RI type was found in 30 and the RII in the rest 3. Three of the 30 RI cases had the reappearance of asexual parasites in the peripheral blood in the first week

(Day 3 to Day 9) after the chloroquine treatment and 27 in the second week (Day 10 to Day 16). The mean number of days from the 1st day of chloroquine administration to the initial clearance of asexual parasitaemia was 2.8 ± 0.3 in the 30 RI cases and in the 23 cured cases as well. These results were shown in Table 2.

The 33 recrudescing patients were treated with 35 mg chloroquine/kg over 3 days to examine on the response of falciparum parasites to the increased dosage of the drug. Although the follow-up period had to be shortened due to the survey schedule, 4 recrudescences (RI in 3, RII in 1) could be found during the period from Day 9 to Day 16. These recrudescences were described in the item of "Incomplete follow-up" of the table. In this survey, 18 acute falciparum patients other than the above-described 56 were found but the follow-up examination to them could not be done during the whole period until Day 16, because of the lack of time, although 25 mg/kg of chloroquine was given to them. Among them, however, 5 RI recrudescence cases could be observed, so they were also listed in "Incomplet follow-up" of the same table.

2. The number of RI recrudescences on each day

Regarding a total of 45 RI cases, including 5 in the incomplete follow-up, to 25 mg/kg of chloroquine obtained through the whole period of this survey, the number of recrudescences was counted each day during the follow-up period. As indicated in Fig. 2, the detection of the earliest recrudescence was done in one case on Day 6, and thereafter the number of recrudescences showed a tendency of increase as days passed.

The mean number of days from the preceding clearance of asexual parasitaemia to the detection of recrudescence was 10.1 ± 1.0 (95% confidence limits) in total of 44 RI cases (one was excluded from the sampling up, as it recrudesced on Day 20).

Chloroquine												Total						
25 mg/kg		1st week					2nd week					RI cases						
Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	20
1st time (1971-1972)							1						2	1			5	1 (10)
2nd time (1973)								1	2	2	2	1	9	2	3	4	9	(35)
Pooled							1	1	2	2	2	1	11	3	3	4	14	1 (45)
													4.7/day		6.0/day			

Mean number of days : $10.1 \pm 1.0^*$

* : The number of days (mean and 95% confidence limits) from the preceding clearance of parasitaemia until the detection of recrudescence

Fig. 2. The number of the RI recrudescences detected on each day after chloroquine administration.

DISCUSSION

Since Moor and Lanier first reported on chloroquine resistance in falciparum patients in 1961, though the observation was carried out in Colombia, South America in 1959, many informations on this subject have been presented from Southeast Asia, and Central and South Americas. In Southeast Asia, the first finding is thought to have been done by Harinasuta *et al.* in 1962 in the central and south parts of Thailand, which was reported in detail in 1965 by them. Since then, the distribution of the 4-aminoquinoline-resistant falciparum strains has been recognized in Malaysia (Montgomery and Eyles, 1963; others), Cambodia (Eyles *et al.*, 1963), and South Vietnam (Powell *et al.*, 1964; others) in addition to Thailand. Further, in recent years, the similar findings were reported from Laos (Ebisawa *et al.*, 1970), Singapore (Ng *et al.*, 1969; Paul *et al.*, 1971), Sumatora of Indonesia (Peters' monograph, 1970), the Philippines (Ramos *et al.*, 1971; Clyde, 1971; Shute *et al.*, 1972), Burma (Clyde *et al.* 1972), and Sabah of Borneo (Clyde *et al.*, 1973).

As for the drug resistance problem on malaria in the Philippines, Ramos *et al.* (1971) pointed out that the chloroquine-resistant falciparum strains existed in the Iwahig Penal Colony of Palawan Island, as they obtained the results that 2 of 20 subjects exhibited the RI recrudescence in the Inagawan Subcolony in 1969 and 19 of 24 examinees also had recrudescence (RII in one, RI in others) in the whole colony area in 1970 to 25 mg/kg. Shute *et al.* (1972) noted the fact that a patient with the amodiaquine-resistant falciparum parasites detected in the Manila area had moved from Palawan Island.

In this survey, 11 of 34 falciparum patients in the 1st time (1971-1972) and 33 of 56 in the 2nd (1973) were found to have recrudescence (RI in 40, RII in 4) to the standard dosage (25 mg/kg over 3 days) of chloroquine. Judging from only this result, it was easily accepted that the falciparum strains resistant or, at least, much less-sensitive to chloroquine had distributed widely in the colony. On the other hand, the fact that a retreatment with an increased dosage (35 mg/kg) of chloroquine to the recrudescing patients could suppress the subsequent recrudescence in most of the patients, might provide us with some criteria on the cause of recrudescence. A possibility that some parasites in patients might escape from the expected action of chloroquine could not be completely removed. Administration of a more increased dosage of chloroquine than 35 mg/kg to subjects was, in fact, hesitated for their physical condition. No difference was found in the initial response of *P. falciparum* to the standard dosage of chloroquine between 2 groups of the RI recrudescence cases and the cured cases. This fact, however, was not thought to have a significant meaning for estimating the chloroquine sensitivity of the falciparum strains which exhibited the RI recrudescence. In this connection, it would be preferable to conduct a single-dose examination with 10 mg/kg of chloroquine for a preliminary test, although the test could not be done due to the limited survey schedule. To avoid misjudgement on the chloroquine sensitivity of the parasites, the so-called drug failure, particularly vomiting of patients, was carefully checked throughout the examina-

tion period.

Although some criteria as mentioned above were left to the future examination, the following results should be noticed: The total number of recrudescences to 25 mg/kg of chloroquine obtained in this survey reached as many as 44 of 90 examinees (48.9%) in which 4 cases of the RII type were included. Further, the fact that 6 recrudescences (RI in 5, RII in 1) to 35 mg/kg of chloroquine could be observed among 44 recrudescing patients to 25 mg/kg of it was to attract the authors' particular attention. Summarizing the data obtained in this survey and the references in the similar field of study published previously by several workers in the Philippines, it could be concluded that the falciparum strains resistant to chloroquine had undoubtedly distributed in the area of the Iwahig Penal Colony.

In addition, it was noticeable that patients with the parasites resistant to chloroquine could be completely cured by treatment with sulformethoxine or sulfamethoxy-pyrazine, either alone or in combination with pyrimethamine.

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フィリピン、パラワン島のイワヒグ地域におけるクロロキン耐性熱帯熱マラリア

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1971年9月より翌年1月まで, および 1973年1, 2月の2回にわたり, フィリピン, パラワン島のイワヒグ 4人部落 (約 390 km², 約 4,000人) において, 熱帯熱マラリア患者を対象にして, クロロキン耐性についての野外調査を実施した. クロロキンの標準投与量は 25 mg 塩基量/kg とし, 3日間に分割, 経口投与を行ない, 原虫検査期間は17日間と定めた. 得られた成績を総合すると次の如くである. (1) 原虫再燃は被検患者 90人中 44人 (48.9%) に検出されそのうち 40人は RI 型を, 4人は RII 型を示した. (2) 上記 RI 再燃患者 44人にクロロキン 35 mg/kg を投与し, うち6人 (RI 型 5人, RII 型 1人) に再燃を認めた. (3) RI 再燃の検出は, 治療開始後6日目の1例がもっとも早期で, 以後日数の経過と共に検出例数の増加が見られた. (4) RI 再燃群と治癒群間には, 無性型原虫の血中より消失するまでの平均日数に有意差を認めなかった. (5) 以上の成績から, 本調査地域にはクロロキン耐性熱帯熱原虫が分布しているものとの結論に達した.

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