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Effectiveness of amodiaquine, sulfadoxine–pyrimethamine, and combinations of these drugs for treating chloroquine-resistant falciparum malaria in Hainan Island, China

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The study was carried out in 1985–86 in Hainan Island where Plasmodium falciparum *is resistant to chloroquine. Fifty cases of falciparum malaria were treated with 1800 mg amodiaquine for 3 days: the cure rate was 65.3%, and the mean time to clear fever and asexual parasitaemia was 30.7 and 60.3 hours, respectively; 34.7% of cases showed RI or RII recrudescence, and one patient's temperature did not come down to normal within 7 days.*

Twenty-one cases were treated with sulfadoxine–pyrimethamine (1500 mg and 75 mg, respectively): 19 were cured, 1 showed RI and another had an S or RI response; the mean time for fever control was 56.1 hours.

Fifty cases were treated with amodiaquine plus sulfadoxine and 49 received amodiaquine plus sulfadoxine–pyrimethamine: the cure rate was 97.9% and 100%, respectively; the mean time for fever clearance was 25.0 and 25.7 hours and for parasite clearance 57.1 and 52.8 hours, respectively. These drug combinations gave much better results for cure and for symptom control than amodiaquine or sulfadoxine–pyrimethamine alone, and may be considered for treatment of chloroquine-resistant falciparum malaria.

Amodiaquine, like chloroquine, belongs to the 4-aminoquinoline group of antimalarial drugs. Cross-resistance between the two had been noted by Young (*1*, *2*); more recently it was reported that in *in vivo* or *in vitro* tests the effect of amodiaquine was superior to that of chloroquine on the Viet-Nam (Marks) strain of chloroquine-resistant *Plasmodium falciparum* (*3*). In Thailand, studies have shown that amodiaquine alone was less effective in the treatment of chloroquine-resistant falciparum infections, compared with the good curative effect from a combination of amodiaquine and tetracycline (*4*, *5*). The present paper evaluates the therapeutic use of four regimens: amodiaquine (AQ), sulfadoxine–pyrimethamine (SP), amodiaquine plus sulfadoxine–pyrimethamine (AQ+SP), and amodiaquine plus sulfadoxine (AQ+S). The study was carried out in 1985 and 1986 in an endemic area of China where *P. falciparum* is resistant to chloroquine.

MATERIALS AND METHODS

Study areas and criteria for selection of patients

The study was conducted in Ledong county of Hainan Island, where chloroquine had been used for more than twenty years, but not amodiaquine. Investigations showed that *P. falciparum* was seriously resistant to chloroquine (82% of cases *in vivo* and 95.5% *in vitro*) (*6*).

Both male and female patients (over 12 years of age) with a body temperature of >37.5 °C (axilla) and parasitaemia of >500 asexual forms per mm^3 were selected. Patients who had received antimalarial drugs within 28 days of the onset of or after a malaria attack

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Table 1. Drug regimens and dosages for treatment of *P. falciparum* malaria

	Drugs			
	Group AQ	Group SP	Group AQ + S	Group AQ + SP
Day 0: dose 1	AQ + placebo: 3 tablets each	SP + placebo: 3 tablets each	AQ + S: 3 tablets each	AQ + SP: 3 tablets each
dose 2 (after 6 h)	AQ: 2 tablets	Placebo: 2 tablets	AQ: 2 tablets	AQ: 2 tablets
Day 1	AQ: 2 tablets	Placebo: 2 tablets	AQ: 2 tablets	AQ: 2 tablets
Day 2	AQ: 2 tablets	Placebo: 2 tablets	AQ: 2 tablets	AQ: 2 tablets
Total dose	1800 mg amodiaquine	1500 mg sulfadoxine + 75 mg pyrimethamine	1800 mg amodiaquine + 1500 mg sulfadoxine	1800 mg amodiaquine + 1500 mg sulfadoxine + 75 mg pyrimethamine

were excluded; this was confirmed by the Dill-Glazko and Bratton-Marshall urine tests for 4-aminoquinolines and sulfonamides, respectively. Patients who were pregnant or who had severe malaria or other complications, mixed infections, or renal insufficiency were also excluded.

Drugs, dosage and regimens

The drugs used were amodiaquine dihydrochloride, each tablet containing 200 mg base; Fansidar,[a] each tablet with 500 mg of sulfadoxine and 25 mg of pyrimethamine; and sulfadoxine, each tablet with 500 mg base. Placebos simulating these drugs were also used. All the drugs were supplied by WHO.

The combinations of drugs and dosages in the four regimens (AQ, SP, AQ+S and AQ+SP) are shown in Table 1. All the drugs had been coded serially in a random distribution by WHO. Allocation of treatment was carried out double-blind and the drugs were always administered under supervision.

Examination and assessment of efficacy

All subjects were followed up for 28 days. Data on each patient included in the trial were recorded using a WHO questionnaire. These included the results of physical examination, haematology (including haemoglobin, erythrocyte count, haematocrit (erythrocyte volume fraction), and total WBC count as well as the differential count), urine test (including albumin, glucose, bilirubin, urobilinogen, WBC and casts), stool examination for parasite ova, and ECG examination. The patient's body temperature was taken every 6 hours until two days after it became normal (37 °C or under) and then twice a day for 7 days. Thick blood smears were examined twice a day till two days after the disappearance of asexual parasites, and then once daily for 7 days. Measurement of body temperature as well as parasitological and other laboratory examinations were done on days 14, 21, and 28. Blood examinations of suspected recrudescent cases were carried out when necessary. Urine tests for amodiaquine and sulfonamide were performed 48 hours after each drug's administration to determine the level of absorption.

Assessment of efficacy was based on standard WHO criteria (*7*) for chloroquine resistance. Patients with clearance of asexual parasitaemia and other signs and symptoms within 7 days and with no recrudescence for 28 days were considered as cured.

Tests to assess the sensitivity of *P. falciparum* to chloroquine and amodiaquine were performed using the WHO *in vitro* microtechnique on some cases prior to drug administration (*8*).

[a] Hofmann-La Roche, Basle, Switzerland.

RESULTS

Clinical effectiveness

A total of 169 malaria cases, of which 117 were autochthonous (61.2%) and 52 nonimmune nonlocal cases (30.8%) were admitted to the study in the four groups. There were 71 cases (42.0%) with a history of malaria. The mean initial parasite density was 27 605 per mm^3 (range, 500 to 207 090 per mm^3). Prior to drug administration, 104 patients (61.5%) had a body temperature between 37.5 °C and 39 °C while 65 (38.5%) had temperatures between 39.1 °C and 40.6 °C; there were 86 cases (50.9%) with splenomegaly.

AQ group. Fifty cases were included in this group and 49 of them were followed for 4 weeks. After treatment, the fever in 24 cases (48%) became normal within 24 hours; in 15 cases (30%) it took 24–48 hours, and in one case the fever did not fall for a week. The mean time for disappearance of fever in 49 cases was 30.7 hours (range, 15–84.5 hours), and the mean asexual parasite clearance time was 60.3 hours (range, 27.3–103.5 hours). Of the 50 cases, 32 (65.3%) were cured (S), 14 (28.6%) showed recrudescence at the RI and 3 (6.1%) at the RII level; one case did not return for follow-up at 4 weeks and would presumably have fallen into the S or RI group (Table 2). All 14 RI cases were associated with delayed recrudescence; in 7 of them the reappearance of parasitaemia was in the third week and in 6 cases in the fourth week.

SP group. Twenty-one cases were admitted to this group and 20 of them were observed for 4 weeks. The body temperature in 3 cases (14.3%) and 5 cases (23.8%) became normal within 24 hours and 24–48 hours, respectively. The mean time to clear fever was 56.1 hours (range, 2.67–109 hours), which was longer than in the AQ group. The mean asexual parasite clearance time was 61.1 hours (range, 32.7–112 hours), which was similar to that in the AQ group. Out of the 21 cases, 19 (95%) were cured (S), one showed RI recrudescence, and one was presumably S or RI.

AQ+S group. Fifty cases were included in this group and 47 of them were followed for 4 weeks. After treatment, the temperature in 28 cases (56%) returned to normal within 24 hours and in 16 cases it took 24–48 hours. The mean time to clear the fever was 25 hours (range, 2–102.5 hours), and the mean asexual parasite clearance time was 57.1 hours (range, 10–105.7 hours). In this group, 46 (97.9%) were cured (S) and 1 (2.1%) showed RI recrudescence; 3 cases did not return for follow-up and would have been either S or RI.

AQ+SP group. Forty-six cases of the 48 in this group were observed for 4 weeks. The mean time to clear fever was 25.7 hours (range, 2–98.3 hours), which was similar to that in the AQ group. The mean asexual parasite clearance time was 52.8 hours (range, 28–152.5 hours), which was less than in the AQ group. All the cases in this group were cured (S); the two who did not return for follow-up were presumably either S or RI.

Both the AQ+SP and the AQ+S groups showed the same good effects of treatment on both autochthonous and nonlocal cases, with no significant difference between the two regimens. But the AQ and SP regimens showed a good effect on autochthonous cases and a less good effect on nonimmune nonlocal cases. In the AQ group, there were 32 cases from the local population; the mean time for them to clear the fever was 21.7 hours, the mean parasite clearance time was 56.4 hours, and 25% of them were resistant cases. Eighteen cases were from the nonlocal population; their mean time to clear fever was 48.4 hours and mean parasite clearance time was 67.7 hours based on 17 cases; 50% of them were resistant cases and there was one case whose fever did not come to normal within 1 week. There were 13 autochthonous cases in the SP group; their mean time to clear fever was 48.2 hours, mean parasite clearance time was 55.8 hours, and all were cured. Eight cases were from the nonlocal population; their mean time to clear fever was 69 hours, mean parasite clearance time was 69.6 hours, 6 were cured, 1 showed an RI response, and 1 case was presumably S or RI.

Appearance of gametocytes

Prior to drug administration, there were 19 cases (11.7%) with gametocytaemia in the four groups. After treatment, the appearance of gametocytes was detected in these groups within 28 days as follows: 25 cases (51%) in the AQ group, 20 (95.2%) in the SP

Table 2. Effectiveness of treatment of *P. falciparum* malaria with the four drug regimens

Drug regimen	Proportion of cases completing 4 weeks	No. cured	Recrudescence			Fever clearance			Parasite clearance		
			RI	RII	RIII	No.	Mean time ± SD (hours)	*t*-test	No.	Mean time ± SD (hours)	*t*-test
AQ+SP	46/48	46 (100)[a]	0	0	0	48	25.7 ± 19.9		48	52.8 ± 22.1	
AQ	49/50	32 (65.3)	14	3	0	49	30.7 ± 24.4	$P>0.05$	47	60.3 ± 20.7	$P<0.05$
SP	20/21	19 (95.0)	1	0	0	21	56.1 ± 28.4	$P<0.01$	21	61.1 ± 20.9	$P>0.05$
AQ+S	47/50	46 (97.9)	1	0	0	50	25.0 ± 22.4	$P>0.05$	50	57.1 ± 20.2	$P>0.05$

[a] Figures in parentheses are percentages.

group, 20 (42.6%) in the AQ+S group, and 23 (50%) in the AQ+SP group.

Adverse reactions

The main adverse reactions were vomiting and sinus bradycardia (on the ECG) (Table 3). The frequency of vomiting was usually once; only one case had repeated vomiting six times. Two cases with no history of stomach complaints had coffee-like vomitus, but recovered after treatment with haemostatics. Most of the adverse reactions were mild and did not require special treatment.

In vitro *sensitivity of* P. falciparum *to chloroquine and amodiaquine*

By *in vitro* testing, 70 (68%) out of 103 cases showed resistance to chloroquine and 9 (37.5%) out of 24 cases showed resistance to amodiaquine.

DISCUSSION

Although the results of using amodiaquine alone for the treatment of falciparum malaria in chloroquine-resistant endemic areas were better in Hainan Island than in Thailand (S. Noeypatimanond, personal communication, 1981), Zanzibar (*9*) or Panama (*2*), 34.7% of the cases (nonlocals comprising 50% of the population) showed resistance to amodiaquine and an RII response. The AQ group took longer to clear the parasitaemia than the AQ+SP group. In one case the fever did not come down to normal within a week; it is therefore not advisable to use amodiaquine alone for the treatment of chloroquine-resistant malaria.

Sulfadoxine–pyrimethamine gave good results with a cure rate of 95%, which was similar to the reports from other countries from 1964 to 1970 (*10*) and much better than the results from Thailand in 1978. This may be because this drug combination had never been used on a large scale in Hainan Island. However, the mean time to clear the fever in the SP group (56.1 hours) was much longer than that in the AQ+SP group (25.7 hours). Thus, amodiaquine plus sulfadoxine–pyrimethamine or sulfadoxine was an effective treatment regimen, as indicated by our results from both local and nonlocal populations: the mean fever clearance time was 25.7 and 25.0 hours, and the cure rate was 100% and 97.9% in the AQ+SP and AQ+S groups, respectively, with no significant statistical difference. These results are better than those of amodiaquine plus tetracycline in Thailand (*4, 5*).

After drug administration, the rate of gametocyte appearance was very high in each group, especially the SP group; it is suggested that primaquine may be required to control transmission of gametocytes with this regimen.

Adverse reactions in all groups were mild and did not interrupt the study or our observations. Hatton et al. (*11*) reported the occurrence of severe neutropenia in malaria patients treated with amodiaquine; one should therefore be on the look-out for this complication when using this drug.

In the 1960s, Ren Daoxing et al. (*12*) compared the effectiveness of amodiaquine and chloroquine and found that chloroquine was superior in China. Our results do not confirm their conclusion, which presumably is due to a change in the sensitivity of *P. falciparum* to these drugs.

Chemotherapy of resistant falciparum malaria is one of the urgent problems to be solved. In recent years, resistance to piperaquine phosphate (*14*), after the emergence of chloroquine-resistant strains (*13*), was found in Hainan. Owing to the shortage of ef-

Table 3. Frequency of adverse reactions in the four treatment groups

Drug group	No. of cases	No. of adverse cases	No. of adverse reactions						
			Nausea	Vomiting	Diarrhoea	Abdominal pain	Dizziness	Headache	Sinus bradycardia
AQ	50	18 (36.0)[a]	5	10	2	1	0	0	9
SP	21	9 (42.9)	7	2	2	7	3	6	0
AQ+S	50	13 (26.0)	1	8	2	3	0	0	6
AQ+SP	48	20 (41.7)	2	11	0	1	1	1	8

[a] Figures in parentheses are percentages.

fective antimalarial drugs, further studies of combinations of amodiaquine with sulfadoxine–pyrimethamine or sulfadoxine, or with other drugs of quick effect after a short course, such as artemether or pyronaridine are required. The use of amodiaquine and sulfadoxine (including sulfadoxine–pyrimethamine), either individually or in combination, should be subject to careful monitoring of side-effects.

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RÉSUMÉ

EFFICACITÉ DE L'AMODIAQUINE, DE LA SULFADOXINE-PYRIMÉTHAMINE ET DES ASSOCIATIONS DE CES MÉDICAMENTS CONTRE LE PALUDISME À FALCIPARUM CHLOROQUINO-RÉSISTANT DANS L'ÎLE DE HAINAN (CHINE)

Une étude comparative en double aveugle a été menée en 1985–1986 dans l'île de Hainan, où *Plasmodium falciparum* est résistant à la chloroquine. Cinquante malades atteints de paludisme à falciparum ont été traités avec 1800 mg d'amodiaquine pendant trois jours: le pourcentage de guérison a été de 65,3% (50% seulement chez les non-autochtones); la disparition de la fièvre et de la parasitémie asexuée a demandé en moyenne 30,7 h et 60,3 h respectivement; il y a eu recrudescence de type RI ou RII dans 34,7% des cas. Chez un patient, la température n'est revenue à la normale qu'au bout de sept jours.

Un autre groupe de 21 patients a reçu des comprimés de sulfadoxine–pyriméthamine (1500 mg et 75 mg respectivement): la fièvre a disparu au bout de 56,1 h en moyenne et la parasitémie asexuée au bout de 61,1 h; 19 patients ont été guéris, un a présenté une réponse de type RI, et un autre une réponse de type S ou RI.

D'autre part, 50 patients ont été traités avec une association d'amodiaquine et de sulfadoxine et 49 avec une association d'amodiaquine et de sulfadoxine–pyriméthamine. Dans le premier cas, la fièvre a disparu en 25,0 h, les parasites sanguins asexués ont été éliminés en 57,1 h et le taux de guérison a été de 97,9%. Dans le deuxième cas, la fièvre a disparu en 25,7 h et la parasitémie en 52,8 h, tandis que le taux de guérison était de 100%. L'effet de ces deux associations de médicaments a été plus rapide que celui de l'amodiaquine ou de la sulfadoxine–pyriméthamine utilisées isolément, en ce qui concerne aussi bien la suppression des symptômes que le traitement radical. On peut donc envisager de les utiliser pour le traitement du paludisme à falciparum chloroquino-résistant.

A la suite du traitement, on a observé une gamétocytémie relativement élevée dans les quatre groupes, notamment dans le groupe traité avec la sulfadoxine–pyriméthamine, où des gamétocytes ont été détectés chez 95,2% des patients. Dans tous les groupes, les effets secondaires ont été peu importants.

La sensibilité de *P. falciparum* à la chloroquine et à l'amodiaquine a été déterminée par micro-épreuve *in vitro*; on a observé une résistance à la chloroquine dans 70 cas sur 103 (68%), et à l'amodiaquine dans 9 cas sur 24 (37,5%).

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