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RESISTANT PLASMODIUM FALCIPARUM INFECTION FROM SAMARINDA, KALIMANTAN (INDONESIA)

by

J. Verdrager[1] and Arwati Loekman[2]

Introduction

Resistance of Plasmodium falciparum to chloroquine in Indonesia was mentioned by Peters (1970), quoting from a personal communication of Soerone (1968) "In the region of Pakanbaru in the Indonesian Island of Sumatra at least one RI response appears certain, but other patients with acute falciparum malaria have responded normally to chloroquine therapy". From the Caltex hospital in Rumbai, Pakanbaru, originated information that in this region of the Indonesian Island of Sumatra at least one RI response appears certain, but that other patients with acute falciparum malaria have responded normally to chloroquine. The follow-up of P. falciparum infections treated in this hospital shows that all were fully sensitive to 4-aminoquinolines and that the above statement was based on a misunderstanding.

In 1973 there were rumours of P. vivax resistance to chloroquine (erythrocytic forms) in Timor. Despite careful examination of the duplicate slides, both in the Jakarta Malaria Reference Laboratory and in the WHO Malaria Reference Laboratory, Epsom, England, no parasites could be found in the slides said to show resistant parasites.

In October 1973 a Government/USA-NAMRU team visited the same area and carried out the WHO sensitivity test. All P. vivax and P. falciparum cases responded satisfactorily to chloroquine (1500 mg base).[3] In all 15 cases of vivax malaria so investigated, the parasites disappeared within 48 hours; in 11 patients they disappeared within 24 hours, i.e. after having received only the first dose of 10 mg base chloroquine/kg. P. falciparum asexual forms also disappeared within 72 hours in the 33 cases studied. The extended 28 days test was not performed.

WHO sensitivity tests were also carried out in North Sumatra by another Government/USA-NAMRU team. Results were similar, with no evidence of resistance in P. falciparum or P. vivax.

The following case history appears to be therefore the first documented report of resistance to 4-aminoquinolines in a strain of P. falciparum from Indonesia.

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[1] WHO; Medical Officer.

[2] Chief, Malaria Control Programme, Indonesia.

[3] Cyrus-Gundelfinger, personal communication.

Case history

The patient Paryadi, a young adult male, age 20 years, weight 58 kg, was found positive (*P. falciparum*) on 17 May 1973 in Bantul Regency (Yogyakarta Province), shortly after returning from Kalimantan.

He was given a standard radical treatment consisting of 1500 mg of amodiaquine base and 45 mg primaquine over a period of three days, from 18 to 20 May. On 18 June he was found again positive and given a second standard radical treatment from 23 to 25 June.

On 13 July he was again found positive and given a third similar radical treatment but this time the amodiaquine tablets were given by and swallowed in the presence of one of us (J.V.). Duplicate slides were collected and the parasite count was carried out. On 7 August he was again found positive and a fourth radical treatment was given from 10 to 12 August.

On 1 September he was once more positive. This time 1500 mg chloroquine base were given and swallowed in the presence of one of the authors (J.V.). Duplicate slides were collected and the parasite count was read. On 27 September he was once again found positive. Treatment was postponed to allow the isolation of the strain with the assistance of NAMRU.

A summary of the drug treatment is shown in Table 1. Over a period of five months from 17 May to 14 October the patient had received a total of 12 450 mg 4-aminoquinolines base (10 350 mg amodiaquine and 2100 mg chloroquine), 350 mg pyrimethamine and 225 mg primaquine. The fact that the drugs were given under supervision of one of the authors or another responsible supervisor living in the same Kampong, the rapid disappearance of the asexual forms after the schizontocidal treatment, and the rapid disappearance of the gametocytes after the administration of primaquine, indicate that most, if not all, of the medicaments were taken.

The infection was terminated by administering a single dose of the combination of 1.0 g sulfadoxine and 50 mg pyrimethamine on 22 October 1973.

The blood samples taken from the patient on 12 October were sent, through a NAMRU-TAMU Research Unit, to Bethesda US Naval Hospital for inoculation into volunteers. Unfortunately these samples were lost *en route*.

Sensitivity tests

Amodiaquine

After having received on 13 July a presumptive treatment consisting of 450 mg amodiaquine base and 50 mg pyrimethamine, the patient, with an already low asexual parasitaemia, was given the standard amodiaquine dose by the WHO malariologist. The asexual forms rapidly disappeared, but on day 19 the patient was found to have again a high parasitaemia (10 000 trophozoites per mm^3).

Details, including the action of the primaquine on the gametocytes, are given in Table 2 and illustrated in Fig. 1.

Chloroquine

After having received on 1 and 3 September 450 mg amodiaquine base plus 50 mg pyrimethamine and 600 mg amodiaquine base respectively the patient had a very low asexual parasitaemia and was given the standard chloroquine dose by the WHO malariologist. The remaining asexual forms disappeared very rapidly, but on day 22 the patient was found to have again a moderate parasitaemia (1000 trophozoites per mm^3). Details are given in Table 3 and illustrated in Fig. 2.

No urine test was carried out as the essential reagents were not available in the Province, but there was neither vomiting nor diarrhoea.

Origin of the case

The patient from Kampong Gedongan (Yogyakarta Province, Java), left his village for Kalimantan island in April 1972 and returned on 5 May 1973. He made the outward trip by bus to Surabaya, then by boat to Samarinda (see map).

In Kalimantan the patient worked for two private Indonesian companies building bridges and schools. He stayed first on the outskirts of Samarinda then in Loa Janan and Segiri Kecamatan. In Loa Janan he worked in a forest area which can be reached by riverboat and on foot in two hours from Samarinda. Here he experienced at least three severe attacks of fever which were treated by injections and tablets. Other symptoms were headache, rigor and sweating, but no vomiting.

There is no malaria control in this area, control measures in Indonesia being mostly limited to the islands of Java and Bali. On the other hand Kampong Gedongan in Yogyakarta Province where this case was discovered, is located in a special study area in which the houses are sprayed twice a year with DDT and where an effective surveillance system is maintained, including active and passive case detection and epidemiological investigations. This system, which also includes the systematic examination of persons returning from other Provinces, revealed, in addition to one imported P. vivax case from Gunung Kidul in August, two other cases in 1973.

Other cases found in the same Kampong

The other two cases detected in Kampong Gedongan, Poniman and Amad Jumeri are friends of the patient. They also went to Kalimantan and worked there approximately in the same area but for a shorter period (five months). Both were detected on 10 May, five days after their return from Kalimantan and both showed P. vivax parasites.

It is interesting that both had recrudescences of P. falciparum after receiving radical treatment for P. vivax. Further recrudescences occurred after repeated radical treatments and the infections had to be terminated with the association sulfadoxine and pyrimethamine.

Both cases were obviously mixed infections in which P. vivax predominated, the RI resistant P. falciparum appearing only after the radical cure of P. vivax. In one (A.J.) P. falciparum rings started to appear two days after the completion of the 14-day course of primaquine.

It is significant to note that there were no similar recrudescences detected amongst other imported or indigenous cases followed up in the special study area of the Province of Yogyakarta. On the other hand, resistant strains of P. falciparum have already been confirmed in Sabah (WHO, 1973)[1] located north of East Kalimantan (see map). One imported suspect resistant case from Tarakan has also been mentioned by Van Dijk (personal communication).

Further studies will be carried out to delineate the infected area of Kalimantan and to identify the vector (which as in Sabah could be Anopheles balabacensis balabacensis) with the objective of applying remedial measures.

Conclusion

The first case of resistance to 4-aminoquinolines in P. falciparum is reported from Indonesia.

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[1] Wld Hlth Org. techn. Rep. Ser., No. 529.

After a normal initial response the asexual parasites were found to be resistant at the RI level to a standard regimen of 1500 mg amodiaquine base and to a standard regimen of 1500 mg chloroquine base.

The infection was contracted near Samarinda in the eastern part of Kalimantan.

ACKNOWLEDGEMENTS

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They are also grateful to Dr Sulianti Saroso, Director General of Communicable Disease Control, for her comments and her suggestion to publish this report.

RESUME

On signale, pour la première fois en Indonésie, une résistance de Plasmodium falciparum aux amino-4 quinoléines. Le premier cas, celui d'un homme de 20 ans, a été décelé dans la régence de Bantul, province de Yogyakarta. Les parasites asexués, après avoir tout d'abord normalement répondu au traitement, se sont révélés résistants au degré RI avec des posologies normales de 1500 mg d'amodiaquine-base et 1500 mg de chloroquine-base respectivement. Il a été établi que l'infection avait été contractée près de Samarinda, dans l'est de Kalimantan (ex-Bornéo) où le sujet avait précédemment travaillé. Dans la régence de Bantul, on a également dépisté deux cas de mono-infection apparente par P. vivax, et les deux sujets avaient également travaillé près de Samarinda. Dans ces cas, P. vivax a disparu après un traitement radical, mais P. falciparum a été observé peu après la fin du traitement et s'est révélé résistant aux amino-4 quinoléines au degré RI. Dans tous les cas on a pu mettre fin à l'infection par P. falciparum en administrant une dose unique de l'association 1 g de sulfadoxine et 50 mg de pyriméthamine.

REFERENCES

Peters, W. (1970) Chemotherapy and Drug Resistance in Malaria, London Academic Press

World Health Organization (1973) Chemotherapy of Malaria and Resistance to Antimalarials, Wld Hlth Org. techn. Rep. Ser., No. 529

TABLE 1. SUMMARY OF MEDICATION GIVEN TO PATIENT PARYADI

Date	Parasites	Drug doses (in mg base)				Remarks
		amodiaquine	pyrimethamine	primaquine	duration	
10 May	Negative	450	50	-	Single dose	Symptomatic
17 May	F++	450	50	-	Single dose	Symptomatic
18-20 May	-	1 500	-	45	Three days	
18 June	F+++Fg++	450	50	-	Single dose	Symptomatic
23-25 June	-	1 500	-	45	Three days	
2 July	Negative	450	50	-	Single dose	
13 July	*	450	50	-	Single dose	Symptomatic
19-24 July	*	1 500	-	45	Six days	Amodiaquine given by WHO Medical Officer
1 Aug.	*	-	50	-	Single dose	
7 Aug.	*	600	-	-	Single dose	Symptomatic
10-15 Aug.	*	1 500	-	45	Six days	
1 Sept.	*	450	50	-	Single dose	Symptomatic
3 Sept.	*	600	-	-	Single dose	
5-10 Sept.	*	1 500 (chloroquine)	-	45	Six days	Chloroquine given by WHO Medical Officer
29 Sept.	*	450	-	-	Single dose	
13 Oct.	F++	600 (chloroquine)	-	-	Two days	
22 Oct.	F+	-	50	-	Single dose	With 1000 mg sulfadoxine

* See details in Table 2.

Particulars on drugs used (tablets):

amodiaquine = Camoquin, Parke-Davis, 150 mg base
pyrimethamine = Daraprim, Burroughs-Wellcome, 25 mg
primaquine = Primaquine, Parke-Davis, 15 mg
chloroquine = Nivaquine, Specia, 100 mg base
sulfadoxine = Fansidar, Roche, 500 mg plus 25 mg pyrimethamine.

TABLE 2. RESULTS OF TEST FOR P. FALCIPARUM STRAIN SENSITIVITY TO A STANDARD DOSE OF AMODIAQUINE IN PATIENT PARYADI

Date	Day	Parasites				Drug dose (mg base)	Remarks
		Trophozoites		Gametocytes			
		Count*	per mm^3	Count*	per mm^3		
13 July	-7	196	1 372	0	0	amodiaquine 450 & pyrimethamine 50	Symptomatic
19 "	0	15	105	1	7	amodiaquine 600	amodiaquine
20 "	1	9	63	8	56	amodiaquine 600	given by WHO
21 "	2	0	0	20	140	amodiaquine 300	Medical Officer
22 "	3	0	0	30	210	primaquine 15	
23 "	4	-	-	-	-	primaquine 15	
24 "	5	0	0	20	140	primaquine 15	
25 "	6	0	0	4	28		
26 "	7	0	0	0	0		
27 "	8	0	0	0	0		
28 "	9	0	0	0	0		
29 "	10	0	0	0	0		
30 "	11	0	0	0	0		
31 "	12	0	0	0	0		
1 Aug.	13	0	0	0	0	pyrimethamine 50	
2 "	14	0	0	0	0		
3 "	15	0	0	0	0		
4 "	16	-	-	-	-		
5 "	17	-	-	-	-		
6 "	18	-	-	-	-		
7 "	19	1 440	10 080	0	0	amodiaquine 600	Sick since 5 Aug.
8 "	20	-	-	-	-		
9 "	21	-	-	-	-		
10 "	22	55	385	0	0	amodiaquine 600	
11 "	23	0	0	2 only seen in thick film		amodiaquine 600	
12 "	24	0	0	1 only seen in thick film		amodiaquine 300	

* Count per 1000 leucocytes.

TABLE 3. RESULTS OF TEST FOR P. FALCIPARUM STRAIN SENSITIVITY TO A STANDARD DOSE OF CHLOROQUINE IN PATIENT PARYADI

Date	Day	Parasites				Drug dose (mg base)	Remarks
		Trophozoites		Gametocytes			
		Count*	per mm^3	Count*	per mm^3		
1 Sept.	-4	450	3 150	0	0	amodiaquine 450 & pyrimethamine 50	Sick this day
2 "	-3	-	-	-	-		
3 "	-2	50	350	0	0	amodiaquine 600	
4 "	-1	15	105	0	0		
5 "	0	3	21	1 only seen in thick film		chloroquine 600	chloroquine given by WHO Medical Officer
6 "	1	0	0	1 only seen in thick film		chloroquine 600	
7 "	2	0	0	2 only seen in thick film		chloroquine 300	
8 "	3	0	0	3	21	primaquine 15	
9 "	4	0	0	2	14	primaquine 15	
10 "	5	0	0	1 only seen in thick film		primaquine 15	
11 "	6	0	0	2 only seen in thick film			
12 "	7	0	0	1 only seen in thick film			
13 "	8	-	-	-	-		
14 "	9	-	-	-	-		
15 "	10	0	0	0	0		
16 "	11	-	-	-	-		
17 "	12	-	-	-	-		
18 "	13	0	0	0	0		
19 "	14	-	-	-	-		
20 "	15	-	-	-	-		
21 "	16	0	0	0	0		
22 "	17	-	-	-	-		
23 "	18	-	-	-	-		
24 "	19	0	0	0	0		
25 "	20	-	-	-	-		
26 "	21	-	-	-	-		
27 "	22	110	770	0	0		asymptomatic (except headache)
28 "	23	-	-	-	-		
29 "	24	45	315	0	0	amodiaquine 450	
30 "	25	15	105	0	0		
1 Oct.	26	5	35	0	0		
2 "	27	8	56	0	0		Treatment delayed for strain isolation
3 "	28	3	21	0	0		
4 "	29	4	28	0	0		
5 "	30	2	14	4	28		

* Count per 1000 leucocytes.

FIG. 1 EFFECT OF AMODIAQUINE, PRIMAQUINE & PYRIMETHAMINE ON A P. FALCIPARUM STRAIN FROM SAMARINDA (KALIMANTAN)

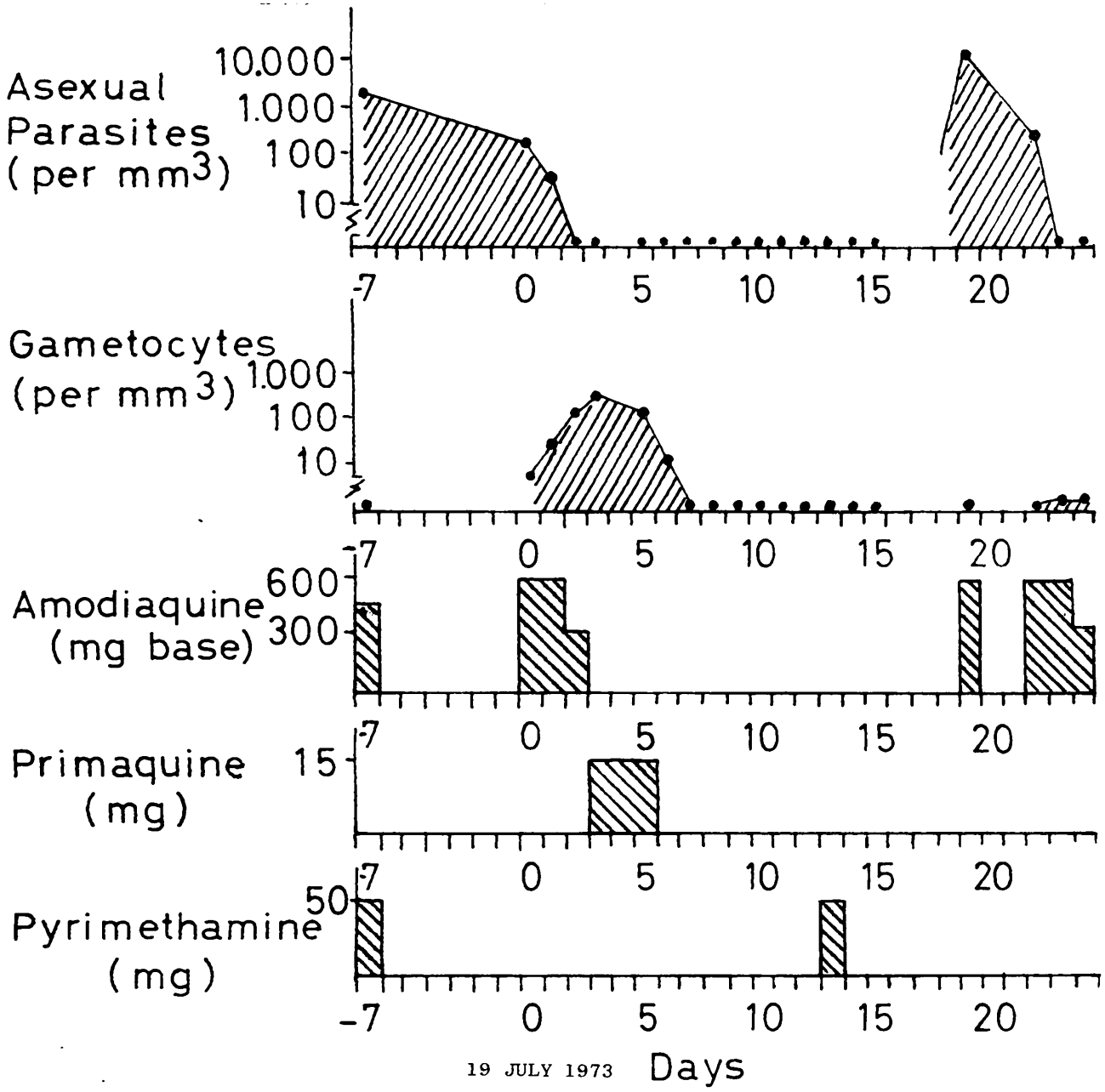
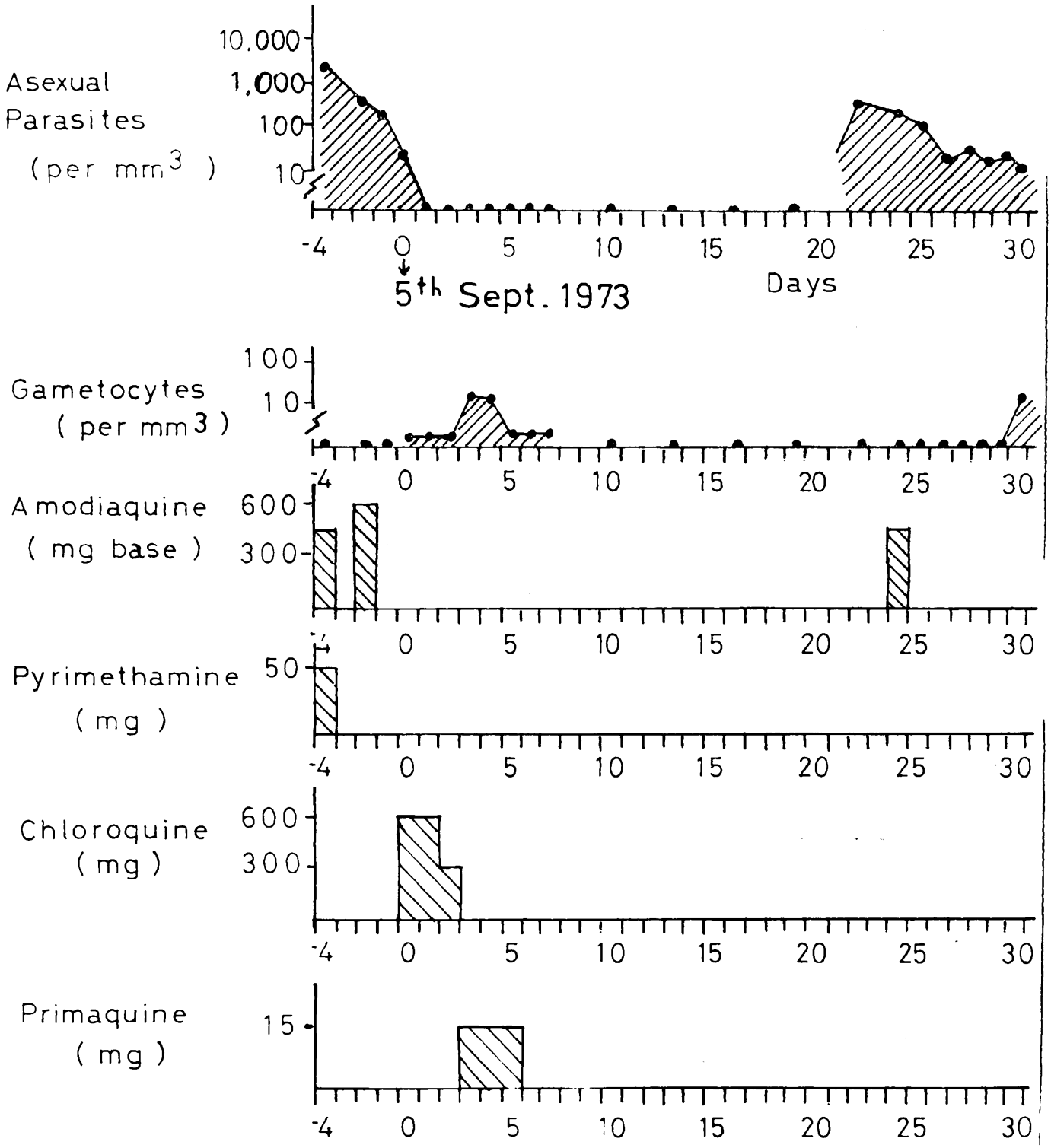
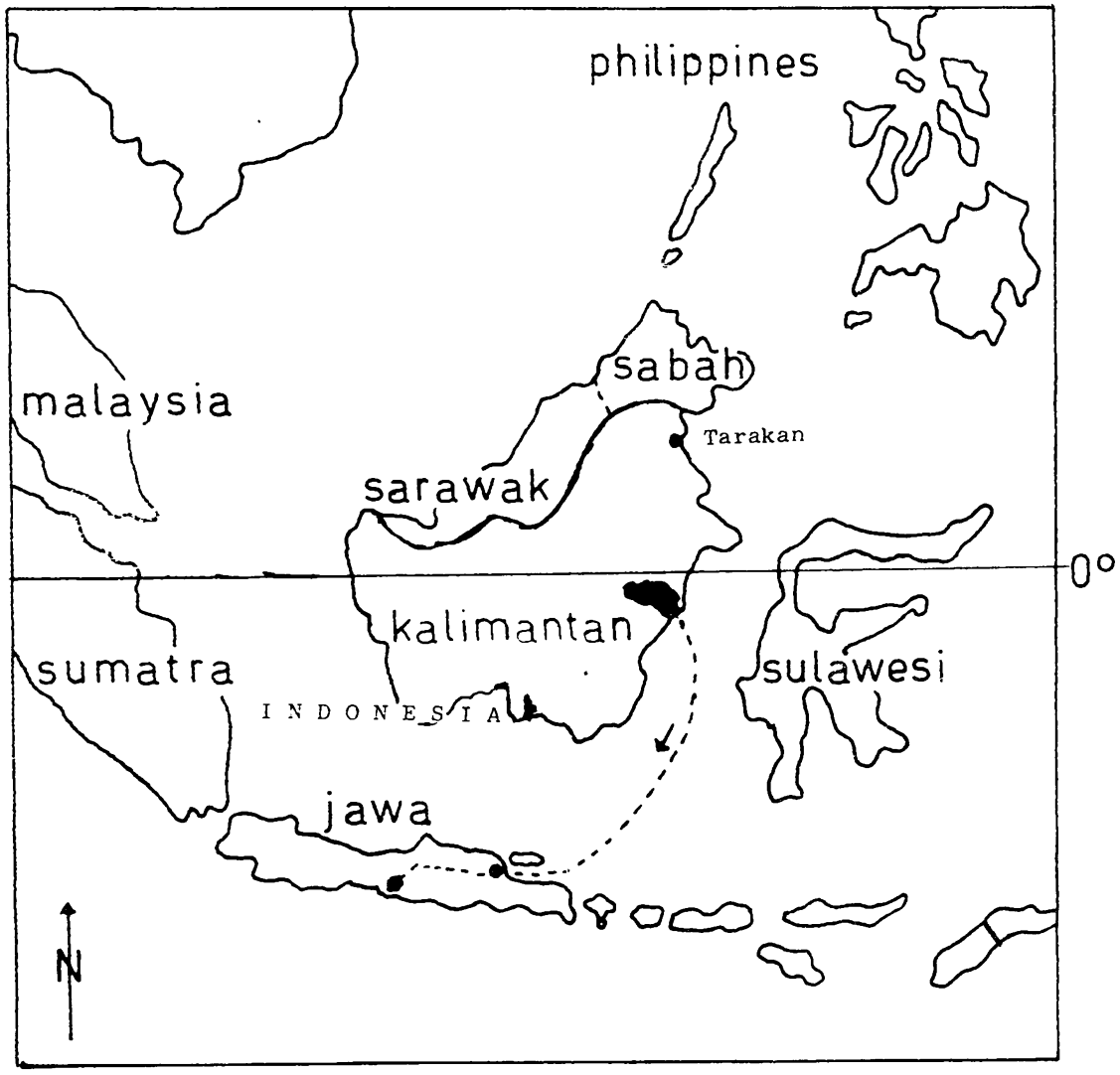


FIG. 2 EFFECT OF AMODIAQUINE, PYRIMETHAMINE, CHLOROQUINE & PRIMAQUINE ON A P. FALCIPARUM STRAIN FROM SAMARINDA (KALIMANTAN)





area in which infection occurred

itinerary followed by reported case from Samarinda to Yogyakarta via Surabaya

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