TREATMENT OF VIVAX MALARIA WITH A SINGLE DOSE OF SULPHADOXINE AND PYRIMETHAMINE (FANSIDAR)

J T Ponnampalan
H A Frank

SYNOPSIS

Chemotherapy is the mainstay of treatment in malaria infections which continue to cause increasing morbidity and mortality rates in developing countries in view of the widespread distribution of chloroquine resistance due to P. falciparum. However, there is no carefully documented evidence to the effect that P. Vivax has developed resistance to chloroquine. The ideal drug is one that would eradicate all strains & stages of the human malaria parasites. However, such a drug is not available at present. Although Fansidar is very effective against chloroquine resistant strains of P. falciparum in Malaysia, it is less so in the treatment of infections due to P. Vivax as shown in this study.

INTRODUCTION

Malaria is still a disease of great importance in South East Asia. In Malaya, all the cities and larger towns are free from transmission but eradication has not been successful in the rural areas. Statistics has shown a down-ward trend of the disease over the past 10 years. However, the number of malaria cases during 1978 and 1979 has levelled off at a figure of 10,000. This does not include patients seen by general practitioners who do not report on cases of malaria which they have treated. Periods of maximum transmission generally occur between the months of November and February, although in the more remote areas of the country, transmission occurs throughout the year.

Chloroquine resistance in P. falciparum infections is high in Peninsular Malaysia, therefore the need to use a combination of antimalarials for treatment. A combination of pyrimethamine and sulphadoxine (Fansidar) has been shown to be effective against Malaysian strains of P. Falciparum resistant to chloroquine and other antimalarials (1, 2, 3, 4).

LITERATURE REVIEW

Chemoprophylactic studies conducted in a rubber estate situated in the central part of Malaysia showed that there was complete suppression of Plasmodium vivax infections when Fansidar was administered in a dosage of one tablet once a fortnight (1). In a previous study (2), Fansidar given in a single dose once every four weeks was found to

Malaria Research Division
Institute for Medical Research
Pahang Road, Kuala Lumpur
Malaysia

J T Ponnampalam, MD, M Sc.
H S Frank, B Sc.

be less effective, as evidenced by more "breakthroughs" with **P. falciparum** and **P. Vivax.** A combination of sulphadoxine and pyrimethamine was administered in fortnightly doses to 26 school children at Bakau, Gambia for a period of 6 months, resulting in complete suppression (5). A second study in Nigeria further confirmed these findings (6). A further trial in West Malaysia showed that similar doses of sulphomethoxine and pyrimethamine given weekly eliminated chloroquine-resistant **P. falciparum** and were also effective against **P. Vivax (3).** A study was done to evaluate the efficiency of standard doses given at weekly, fortnightly and four weekly intervals in an area of stable **P. falciparum** malaria on 170 natives of Ilorin Area, Nigeria (6). The results showed that weekly and fortnightly doses were more effective in suppression than doses given once every four weeks. The efficacy of weekly and fortnightly doses confirm the statements of Laing (3) that sulphormethoxine included in the combination has a half life of 100 — 200 hours which permit sufficient blood levels to be maintained by weekly doses. However, it was reported later that even lower doses were effective when given fortnightly (2). A trial to study the suppressive effect of Fansidar on Malaria parasitaemia in an area of endemic malaria (a Malaysian rubber estate) was conducted over a period of four months (4). In this trial the drug was given monthly, while weekly chloroquine phosphate was used as a control.

It was observed that there were 4 episodes of parasitaemia in the Fansidar group and 79 episodes of parasitaemia in the control (chloroquine) group throughout the course of the trial. The monthly Fansidar regime had a greater effect in suppressing malaria parasitaemia (both falciparum & vivax) than the weekly administered chloroquine. Recently, Doberstyn and his colleagues have reported their findings about the treatment of P. vivax infection with Fansidar in Thailand (7).

Sulphadoxine is a long acting sulfonamide with a half life of 100 — 200 hours and it is therapeutically effective in low dosage (8). Pyrimethamine belongs to the group of substances which interfere with the synthesis of folinic acid by the malaria parasite, by blocking the action of dihydrofolic acid reductase. Doses of sulphadoxine plus pyrimethamine exerted an enhanced schizontocidal effect as potent as that of chloroquine, attributable to the potentiation of pyrimethamine by the sulfonamide, whereby the combined effect of the two drugs together is greater than the effect of larger doses of either drug separately. The drug is given in a single oral dose and does not posses a bitter taste, a feature which facilitates its acceptance by children. The purpose of this study was to determine the efficacy of this combination in malaria due to P. Vivax.

STUDY POPULATION AND METHODS

Studies were carried out at the General Hospital, the Malaria Division, Institute for Medical Research, Kuala Lumpur, and Gombak Hospital, Selangor. Patients treated at the General Hospital consisted of Malays and Indians, and a few Vietnamese refugees. All the Malays suffering from malaria were members of the Police Field Force who were constantly exposed to infection during their jungle operations in Northern Malaysia. They also had past histories of similar attacks. One of the patients admitted was a male Vietnamese refugee housed at the local camp.. All blood films were examined at the Malaria Division, and treatment with a single dose of Fansidar was instituted if the blood film was positive. Patients were followed up for 28 days or longer with weekly blood examination; if these were negative at the end of 28 days the patients were considered as cured.

* Also known as Sulfadoxine (Fanasil).

The Gombak Hospital, Selangor is about 13 miles from Kuala Lumpur, the capital of Malaysia, and is confined to the treatment of the Orang Asli, commonly referred to as the aborigines of Malaysia. The majority came from malarious areas in deep jungles and could be regarded as "semi-immunes". They are brought to the hospital either by road or helicopter. The whole family was brought in for admission to the hospital, and often more than one member of the family were infected with malaria. Family members of staff working at the hospital who were positive for malaria were also treated at the clinic. They became infected while on tour of duty at the jungle medical posts where they are resident for a period of 3 — 6 months. These were requested to take prophylaxis regularly but the schedule was not adhered to. Children with any other infections (especially upper respiratory tract infections) were taken care of, too. Biscuits and sweets were distributed daily so as to encourage the children to attend the clinic regularly and to stay on for the complete follow-up.

A standard form was used to record species identification, parasite density, dosage schedules and other relevant information.

Peripheral blood smears (both thick and thin) were examined from patients with clinical symptoms suggestive of malaria. Thick smears to assess the effects of the drug on parasitaemia were stained with 10% Giemsa for 10 minutes and parasite counts recorded on the standard form referred to above. Parasites were counted against 200 leucocytes and densities per mm3 estimated accordingly. Blood films were reported as negative if no parasites were seen in 100 microscopic fields. Thin blood smears were carefully examined for species identification. Full blood picture, glucose-6-phosphate dehydrogenase deficiency and liver function tests were carried out on each patient. Liver and spleen were examined in the recumbent position and measured in centimeters, if palpable. Treatment with Fansidar was strictly supervised and the immediate response to therapy assessed by examination of thick blood films daily for 7 days and thereafter at intervals of 5 days from Day 8 to Day 28. Temperatures of patients were recorded on temperature charts. The criteria of apparent cure were the elimination of asexual parasites from the peripheral circulation and complete suppression of fever. Treatment was considered a failure when asexual parasitaemia was still present on Day 7 or if parasites reappeared at any time before Day 28.

Fansidar was administered as a single dose as follows:-

Under 2 years	—	¼ tablet
2 — 4 years	—	½ tablet
4 — 8 years	—	1 tablet
8 — 14 years	—	2 tablets
Adults	—	2 — 3 tablets.

RESULTS

The number of days taken for complete elimination of trophozoites from the peripheral circulation after the administration of Fansidar is shown in Tables 1 & 2. Age, sex and dosage of drugs administered to each patient are also shown. Patients admitted to the General Hospital were all adults between the ages of 20 — 35. Most of them were members of the Police Field Force, while the rest were civilians. Seven of them were Malays, 1 Indian, and one a Vietnamese refugee. Twenty-nine patients treated at the Gombak Hospital were Orang Asli, mainly children, whose ages range from 5 months to 13 years; three of these patients were previously treated for malaria. In both the groups, gametocytes were present in blood films for several days after the onset of therapy. All subjects tolerated the medications well, no serious side effects being observed, except for

Table 1: Aborigine (Orang Asli) patients admitted to Gombak Hospital, Selangor

Patient	Name	Sex	Age (yrs)	Parasitaemia per mm^3 before treatment (DO)		Parasitaemia per mm^3 on Day 1.		No. of days for elimination of Trophozoites and Gametocytes.		No. of days for fever to subside.	Reappearance of parasites before Day 28.	No. of days patient was followed up.
				Trophozoite	Gametocyte	Trophozoite	Gametocyte	Trophozoite	Gametocyte			
1.	S.B.D.	F	7	1680	160	6400	0	6	3	3	Nil	36
2.	M.A.	F	4	200	80	440	80	4	4	afebrile on Day 0	Nil	38
3.	W.S.	F	5	9560	40	blood film not taken		4	4	afebrile on Day 0	Nil	32
4.	A.N.	M	2	9440	1360	blood film not taken		7	6	afebrile on Day 0	P. falciparum Day 28	28
5.	M.B.	M	10	7200	120	blood film not taken		7	10	4	Day 20	-
6.	A.A.	F	12	80	0	1	0	2	2	afebrile on Day 0	Nil	116
7.	K.K.	F	3	400	40	1040	120	3	3	afebrile on Day 0	Nil	34
8.	S.A.	M	5½	8600	0	6960	1240	Persisted for 9 days treated with chloroquine and primaquine on D 9.		Fever persisted until alternative treatment given.	-	-
9.	V.L.	M	3	120	0	0	0	1	1	afebrile on Day 0	Nil	49
10.	B.C.	M	3	7200	160	7960	120	7	7	2	Nil	11 (incomplete follow up).
11.	W.C.	F	10	440	0	80	0	4	-	2	Nil	41
12.	A.G.	F	61	600	0	280	40	3	1	afebrile on Day 0	Nil	55
13.	L.N.	M	4	17,800	0	7280	480	No clearance for 23 days.		5	-	42. Patient treated with chloroquine + primaquine.
14.	B.N.	M	8	1600	0	80	0	2	2	afebrile on Day 0	Nil	31
15.	Z.H.	F	13	1080	40	not	done	2	2	2	Nil	28
16.	L.A.R.	F	12	960	0	600	0	3	-	1	Nil	29
17.	R.A.	M	1	320	280	360	0	9	9	1	Nil	130. Film positive for P. falciparum on D 122.
18.	S.B.A	F	2	440	0	120	0	No clearance on Day 12		afebrile on Day 0	-	48. Treated with chloroquine + primaquine.
19.	A.M.	F	5	760	0	480	0	4	-	afebrile on Day 0	Nil	49
20.	N.Z.	F	4	32,000	400	680	0	2	2	1	28	40
21.	R.A.	F	10	11,120	80	12,840	240	4	2	3	Nil	56. Film positive for P. Vivax.
22.	H.D.	M	6	6,320	280	11,040	320	No clearance of parasites for 14 days.		3	-	Treated with chloroquine + primaquine on D 14.
23.	A.C.	F	4	200	80	440	80	4	4	afebrile on Day 0	Nil	28
24.	K.K.	F	1 yr 8 mths.	480	40	360	40	6	4	afebrile on Day 0	-	14 (incomplete follow up.)
25.	R.N.	F	5½	7,920	40	6,420	0	4	4	2	Nil	28
26.	H.D.B.	F	15	7,920	80	80	80	3	3	afebrile on Day 0	Day 20	Treated with chloroquine + primaquine.
27.	R.H.	M	5 mths	4,720	120	6,800	160	6	6	1	Day 10	Treated with chloroquine + primaquine.
28.	S.Y.M.	F	1	7,600	40	4,560	320	5	5	afebrile on Day 0	Day 7	Treated with chloroquine + primaquine.

Table 2 : Patients admitted to General Hospital, Kuala Lumpur

Patient	Name	Sex	Age (yrs)	Parasitaemia per mm^3 before treatment (D0)		Parasitaemia per mm^3 on Day 1		No. of days taken for elimination of Trophozoites & Gametocytes.		No. of days for fever to subside.	Reappearance of parasites before Day 28.	No. of days patient was followed up.
				Trophozoite	Gametocyte	Trophozoite	Gametocyte	Trophozoite	Gametocyte			
1.	N.M.D.	M	25	2,120	120	7,280	720	7	7	1	Nil	57. Film positive for P. vivax on this day. Treated with chloroquine & primaquine.
2.	Z.M.D.	M	35	3,320	520	3,480	120	2	2	1	Nil	82
3.	B.G.	M	20	3,240	280	5,800	280	4	2	1	Nil	139
4.	J.T.	M	22	10,480	640	1,760	240	4	4	1	Nil	252
5.	M.A.	M	21	8,240	720	3,200	800	3	6	1	Nil	76. Film positive for P. vivax on this day. Treated with chloroquine & primaquine.
6.	P.S.	M	33	11,240	240	blood film not taken		6	7	1	Nil	114. Reappearance of P. vivax; treated with chloroquine & primaquine.
7.	N.H.N	M	25	7,200	80	2,160	80	5	5	1	Nil	28
8.	M.H.M	M	31	12,600	400	2,800	400	6	5	2	Nil	37
9.	T.I	M	30	1,040	670	blood film not taken		2	2	afebrile on admission.	19	51. Treated with chloroquine & primaquine.

mild disturbances like gastric irritation and vomiting in a few of the children.

Among the patients treated at the General Hospital two were incompletely followed up to Day 14 and Day 26 respectively; they were discharged when their peripheral blood films were negative, as they were keen to resume their jobs, and did not attend for further review. Among the Orang Asli patients, 3 were incompletely followed-up; these children were brought to the hospital by their parents who were mainly farmers in the rural areas. Some of them refused to stay on for the complete 28 day follow-up as they had to get back to work.

Nine of the 29 aborigine patients, and three of the 9 patients from the general population showed an increase in parasite density on Day 1, varying anywhere from slight to significant.

It was not uncommon to find that a number of patients were afebrile on the day treatment was commenced. Similarly, when conducting rural surveys in malaria endemic areas it was not unusual to find children leading apparently normal lives with a history of an occasional bout of low grade fever for a day or two but with a significant parasite density. Very often they are not aware that they are suffering from malaria.

Eight of the aborigine patients showed varying degrees of resistance of their vivax infections to Fansidar. None of the patients from the other group showed any evidence of resistance to the drug although two of them had an incomplete follow up.

CONCLUSION

Fansidar was only partially effective in controlling infections due to Plasmodium vivax as determined by the length of time taken for the parasites to be cleared from the bloodstream, and for the fever to subside; it is widely accepted that chloroquine is more effective when considering these aspects as the criteria for response to any drug. Gametocytes were cleared from the peripheral blood anywhere from one to 10 days with the majority of patients showing clearance on an average of 3 — 4 days. Three patients showed clearance of parasites on Day 7, 9 and 10 respectively. Studies in our laboratory have shown that Fansidar is ineffective as a gametocytocidal agent and development proceeds to the stage of sporozoites. From a public health point of view a single dose of primaquine should be administered on the day after the dose of Fansidar in order to prevent infectivity to mosquitoes and spread of the disease.

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