TREATMENT OF FALCIPARUM MALARIA WITH A SINGLE DOSE COMBINATION OF DAPSONE AND PYRIMETHAMINE (MALOPRIM)

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SYNOPSIS

Details are given of 22 cases of acute falciparum malaria treated with a single dose of Maloprim — pyrimethamine 12.5 mg and dapsone 100 mg.

Trophozoites initially cleared from the blood stream within 2 to 3 days of drug administration. Temperature returned to normal on an average of 3 to 4 days.

Recrudescence occured in 7 patients.

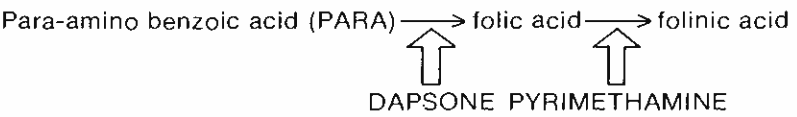
Three patients did not respond to treatment.

INTRODUCTION

Maloprim has been used both in the prophylaxis and treatment of malaria. It is a combination of 2 drugs — pyrimethamine and dapsone (a sulphone). These 2 drugs act synergistically and are therefore effective in lower doses in the supression of parasitaemias. They have been shown to be effective in the therapy of chloroquine — resistant falciparum infections (1).

Pyrimethamine is highly active against blood forms of plasmodia. Dapsone was initially used in the treatment of leprosy when it was noted that patients, though living in an endemic area, showed a lower incidence of malaria than the general population (2). This suggested that the drug was active against asexual forms of the parasite.

Maloprim basically acts as a bacteriostat and prevents the use of certain metabolites essential for normal growth.



Dapsone prevents the incorporation of PABA into folic acid thereby acting as a competitive antagonist.

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The conversion of folic acid to folinic acid is common to both parasite and host, but the effect of pyrimethamine in this step is differential. This is due to the tighter binding of pyrimethamine to the dihydrofolic acid reductase of the parasite than the host. The host has the ability to bypass this step by obtaining folinic acid from dietary sources. Pyrimethamine does not depend on an energy process to enter the parasite and can therefore act on its surface.

Toxic side effects observed previously in the use of the drug have been depression of haemopoiesis due to the interference of the drug in the metabolism of folic acid, haemolysis and agranulocytosis.

The aim of this project is to study parasitaemia and fever trends in patients with Plasmodium falciparum treated with a single dose of Maloprim.

LITERATURE REVIEW

Over the past 2 decades, the prophylaxis and treatment of malaria using the synergistic combination of pyrimethamine and dapsone has been decumented in various parts of the world. This drug combination has been known to provide protection against strains of P. falciparum resistant to the standard antimalarials. Archibald and Rose (2) in a preliminary study, reported the effectiveness of dapsone in the suppression of malaria in Nigeria.

Basu et al. (3) studied the value of dapsone combined with pyrimethamine in the treatment of malaria in India. They found that complete clearance of parasitaemia and termination of fever occurred within 48 — 72 hours when an adult dose of 100 mg dapsone combined with 12.5 mg pyrimethamine was given as a single dose.

Lelijveld (4) in a prophylactic survey in N.E Tanzania, using pyrimethamine and dapsone, showed that at 4 weeks and 10 weeks after the initiation of prophylaxis, all subjects were parasite-free. In addition, none of the fever cases during the 10 weeks period presented a positive blood film.

The suppression of malaria using weekly doses of pyrimethamine with dapsone or sulphormethoxine was investigated by Lucas et al. (5) in a falciparum endemic area in W. Nigeria. In both instances parasitaemias in school children cleared rapidly. After clearance, very occasional cases of scanty Parasitaemia were detected. The drug combination retained its effectiveness throughout the year, and was well tolerated with no serious side-effects.

Laing (6) studied the treatment of overt falciparum malaria with potentiating combinations of pyrimethamine with sulphormethexine or dapsone in the Gambia. In low dosage combinations, pyrimethamine 0.1 mg/kg with either combination exerted total schizonticidal effect within 2 days in most cases. Treatment with the adult equivalent of pyrimethamine 5 mg and dapsone 50 mg or sulphormethexine 100 mg, was completely effective in terminating acute attacks of falciparum malaria in susceptible children. The potent schizonticidal effect of both these combinations, together with the slow rate of excretion suggests its usefulness in prophylaxis when given in weekly or fortnightly doses.

Segal et al. (1) tested the efficacy of the standard dapsone 100 mg — pyrimethamine 12.5 mg combination in suppressing parasitaemia in N.E Thailand. The area was endemic for chloroquine — resistant strains. Weekly doses were given for 26 consecutive weeks. The treatment was found effective in suppressing P. falciparum parasitaemia and associated symptoms. The drug performed better in the suppressive cure of falciparum infections than in vivax infections.

A dapsone — pyrimethamine combination has been used previously as a prophylactic for malaria in different parts of Malaysia. Ponnampalam et al. (7) in a prophylactic survey, found that it gave protection against infection with P. falciparum when taken in adequate doses each week. Occasional breakthrough parasitaemia in low densities due to P. vivax occurred. The drug appeared to have little effect on the exo-erythrocytic stages of the parasite.

MATERIALS AND METHODS

Patients under study were from the Gombak Hospital, the Police Field Force and the General Hospital, Kuala Lumpur. Most of the Gombak Hospital patients were aborigine from jungle-bordered settlements or the jungle areas of West Malaysia where malaria is endemic. Some of the patients had a previous history of malaria. Members of the Police Field Force also operate in jungle areas, and probably contracted malaria there. They are usually advised to take malaria prophylactics, but the regularity with which drugs are taken is not known.

Those admitted to hospital were suffering from acute symptoms. Thick blood films were examined before treatment, and almost daily thereafter for 7 days. In addition, blood pictures were studied before and after treatment. Glucose 6-phosphate dehydrogenase deficiency screening was carried out in each case ,the Motulsky's or Bernstein's test being used. Temperature was monitered daily, and liver and spleen examination were carried out at the time of the blood examinations.

Patients were requested to attend the malaria clinic at the hospital regularly for clinical examination, administration of drugs, examination of blood films and other routine tests. Follow up was carried out for up to 28 days where possible.

The treatment schedule was a single dose of Maloprim. Adults received 3 tablets, each containing 12.5 mg pyrimethamine and 100 mg dapsone. Children aged 8 to 16 received 2 tablets, those between 3 to 7 years had 1 tablet, while those under 2 years were given half tablet.

Patients were seen to by a doctor and the laboratory tests carried out by graduate technicians. Thick blood films stained with 10% Giemsa were examined, parasites counted against 200 white blood cells and density of parasitaemia calculated on the total white cell count.

This study was carried out between May and August, 1980 during which a total of 22 patients with falciparum malaria were treated.

RESULTS

There were 22 cases within the 3 categories of patients under study the majority of whom were aborigines. Thirteen were males and 9 were females. Within the classified age groups (Table 1), the most number of cases occurred amongst children between the ages of 1 and 4 years old.

The response of the parasites to Maloprim, as shown by the clearance rate of trophozoites is demonstrated in Table 1. On average, trophozoites disappeared from

Table 1 CLINICAL DETAILS OF PATIENTS

NO.	NAME	SEX	AGE(YRS)	PARASITE DENSITY PRIOR TO TREATMENT PER MM^3 BLOOD TROPHOZOITES/GAMETOCYTES	NO. OF DAYS FOR BLOOD FILM TO BECOME NEGATIVE FOR TROPHOZOITES	NO OF DAYS BEFORE TEMPERATURE BECAME NORMAL	GLUCOSE-6-PHOSPHATE DEHYDROGENASE ACTIVITY	COMMENTS
1.	A.J.	MALE	8 months	240/0	1	2	normal	P. vivax positive on day 22 Measles on day 12. Alternative treatment given.
2.	A.A.	"	1	7,560/1,060	3	1	normal	Recrudescence on day 9 Alternative treatment given
3.	A.A.	"	1	10,200/0	4	3	deficient	Recrudescence on day 8.
4	Y.N L	"	2	560/160	3	afebrile	normal	P. vivax positive on day 21
5	M.J.	"	2	22,800/6,560	No clearance	7	deficient	Haemoglobinuria after Maloprim. Alternative treatment given.
6.	M.A.	"	3	9,800/0	4	5	deficient	Follow-up until day 28.
7.	R.J.	"	4	135,000/2,600	No clearance on day 5	7	normal	Alternative treatment given.
8.	M.J.	"	15	17,400/0	1	1	normal	Recrudescence on day 37
9	A.P.	"	16	28,000/0	2	2	not carried out	Follow-up until day 14
10.	S.S.	"	19	5,840/0	2	1	normal	Recrudescence on day 24.
11	A.I.	"	21	54,800/40	4	2	normal	Recrudescence on day 20 Alternative treatment given
12.	L.K H	"	22	135,000/0	5	5	not carried out	Follow-up until day 28
13.	J.J.	"	40	320/0	2	afebrile	not carried out	Recrudescence on day 28 Alternative treatment given
14	S.A	FEMALE	8 mths	400/200	3	afebrile	normal	Follow-up until day 15
15.	Z.J.	"	9 mths	3,000/1,560	no clearance on day 9	afebrile	normal	P vivax positive on day 21 Alternative treatment given.
16	N.O.	"	3	840/0	2	8	normal	Follow-up until day 24
17	M.A.	"	4	13,200/0	1	2	normal	Follow-up until day 28
18	Z.D	"	6	128,000/0	7	4	normal	Recrudescence on day 11 Alternative treatment given
19.	R.J	"	7	320/0	2	afebrile	normal	Follow-up until day 25.
20	U A	"	12	6,960/0	3	afebrile	normal	Follow-up until day 14.
21	H.C T.	"	adult	1,120/0	2	afebrile	deficient	Follow-up until day 12
22	W C.C.	"	29	1,240/0	1	1	normal	Follow-up until day 28

the peripheral blood about 2 to 3 days after Maloprim was administered. In 4 cases within 1 family there was no clearance of trophozoites by Day 5, so alternative treatment was given.

Recrudescence occurred in 7 patients. In these cases, initial clearance of asexual stages took place within 1 week of drug administration. Three patients showed early recrudescence — 8 to 12 days, three recrudescened after 20 days, and one showed late recrudescence on day 37. Alternative treatment was administrated to all who had a recrudescence.

In 10 cases, gametocytes showed a tendency to increase in numbers within 1 week of treatment.

Three patients became positive for P. vivax after 3 weeks.

Seven patients were afebrile at commencement of treatment. Amongst those with fever, temperature returned to normal on an average of 3 — 4 days. The clearance of fever tended to take longer in those patients with higher parasite densities eg. 20,000 trophozoites per mm^3 of blood. Amongst the children, pyrexia could also have been attributed to upper respiratory tract infections or common contagious diseases e.g. measles, presenting with malaria.

Four patients showed a deficiency of glucose-6-phosphate dehydrogenase activity. In one such patient whose initial parsitaemia was 22,800/6,500 (trophozoites/gametocytes), haemoglobinuria resulted after Maloprim was taken. Otherwise, the drug was generally well accepted. There were 2 instances of vomiting immediately or shortly after the drug was taken.

Five patients, cases number 2,6,17,18 and 22 had a previous history of malaria. Case 17 had homozygous E abnormal haemoglobin. Case 22 was sickle-cell positive

DISCUSSION

The majority of patients under study were aborigines. They live in jungle settlements where malaria is endemic and malaria eradication is a difficult task for various reasons. The younger age groups suffered acute symptoms to a greater extent. This is probably because acquisition of immunity against malaria increases with age, and they had not reached this status yet. Amongst those from the Police Field Force, some personnel were perhaps non-immunes, and their entry into endemic jungle areas enhanced the possibility of infection.

Trophozoite clearance after a single dose took between 2 to 3 days. This is consistent with the findings of Lucas et al. (5), who had similar results after a single dose of the drug combination. In the work of Basu et al. (3), 10 patients showed clearance of trophozoites in 2 days. There was no recrudescence within the follow-up period ranging from 14 — 28 days. This differs from the present study in that recrudescence did occur here.

Cases, 5, 7 and 15 where parasitaemia persisted were R_2 resistant. Seeing they were from the same family, it is possible that a particular strain of P. falciparum may have caused this. Case 1, 13 and 19 from the same family did not however demonstrate this phenomenon.

Recrudescence occurs not infrequently in drug resistant falciparum malaria. Amongst those who recrudesced, initial trophozoite clearance occurred within 1 week. So drug performance was no different when compared with patients who did not recrudesce. However, a single dose of Maloprim appears to have little or no effect in preventing a recrudescence. It appears partially effective for treatment in the dosage given.

There were 3 cases of a mixed infection due to P. falciparum and P. vivax. Generally under such circumstances, P. falciparum is the dominant parasite. Therefore, when cure is effected for a falciparum infection, P. vivax surfaces. Maloprim does not have any effect on exo-erythrocytic stages of P. vivax, thus break-through parasitaemia occurs (7).

Gametocytes remained in low numbers or disappeared from the blood stream, but in 10 cases numbers increased within 1 week of treatment. On account of this variability it is difficult to assess whether the drug stimulates, represses, or acts indifferently towards gametocytes. It is thought that with Maloprim, gametocytes tend to be in the blood stream for a longer period of time than in cases treated with chloroquine (8).

Amongst those who were G-6-P-D deficient, cases 6 and 20 responded well to treatment. Case 3 recrudesced on day 8. Case 5 showed toxic effects of the drug with clinical signs of haemoglobinuria. This was the only case who demonstrated signs of acute toxicity after a single dose of Maloprim. The drug has previously been known to cause certain haematological disorders, but only with prolonged use (9,10,11). Lucas et al. (5) working on a drug trial with Maloprim, did not find adverse effects of the drug in G-6-P-D deficient patients.

Two patients showed poor acceptability of the drug in that they vomitted it immediately after or within a few hours of ingestion.

Amongst the abnormal blood types, neither sickling nor homozygous E abnormal haemoglobin appeared to have conferred protection against acute falciparum malaria.

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