# RESPONSE OF DRUG-RESISTANT *PLASMODIUM FALCIPARUM* TO COMBINED THERAPY IN PANAMA

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## Introduction

It has been shown recently that *Plasmodium falciparum* malaria infections in Panama are resistant to the 4-aminoquinoline drugs, chloroquine and amodiaquine (Young & Johnson, 1972). Following the failure of these drugs, alternative drug regimens were instituted by the national malaria control organisation, *i.e.* Servicio Nacional de Erradicación de la Malaria, for the treatment of cases in the field and hospital. At the same time, we began a detailed study of the response of the infections to these regimens.

## Materials and Methods

The malarious patients lived near Panama City, Republic of Panama. Most of them were in the Santo Tomás and Children's Hospitals (Hospital del Niño), adjacent to the Gorgas Memorial Laboratory. Initially, those given the combination drugs had been treated previously with one of the 4-aminoquinoline drugs, either chloroquine or amodiaquine. Later the sulphonamide combination regimens were used for the primary treatment of the infection.

The drug regimens for adults were:

| | *Day 0* | *Day 1* | *Day 2* |
|---|---|---|---|
| Sulphadimethoxine (Madribon®) | 1g. | 0·5g. | - |
| or | | | |
| Sulphormethoxine (Fanazil®) | 1g. | 0·5g. | - |
| plus | | | |
| Pyrimethamine (Daraprim) | 50mg. | - | - |
| and | | | |
| Primaquine | - | - | 45mg. |

Children received proportionally lesser amounts based on age.

The taking of the drug was supervised. Thick blood smears were made at 24-hour intervals, stained by the Giemsa method and the parasites enumerated by the Earle-Perez method (1932). Attempts were made to follow the patients daily for seven days and frequently thereafter for a total of 28 days or longer, when possible.

## Results

The parasites were cleared rapidly from the blood stream, on an average of 2·3 days for the sulphadimethoxine combination and 2·5 for the sulphormethoxine (Table I).

Although the infections responded quickly, about one-third relapsed. The relapses appeared between 15 and 35 days after the initiation of treatment, with one exception which occurred 48 days afterwards (Table II).

Of the failures, three were treated with quinine sulphate 650 mg. three times daily for 10 days for adults. In two cases, the parasitaemias were cleared in two and three days respectively. Of these, it was possible to follow one for 28 days during which time no relapses occurred. In the third case, the parasitaemia was not cleared in 15 days (Table III).

Some of the failures were cured by subsequent treatment with the sulphonamide combinations or with amodiaquine.

Not included in Tables I and II was a case (F-2) which had been treated elsewhere with chloroquine 2·1g. base in five days, combined during the first four days with 9g. sulphasoxazole (Gantrisin®); on the fifth, sixth and seventh days, he received 15mg. primaquine daily. The parasitaemia and fever had not been eliminated by the eighth day, at which time we began the regimen of sulphormethoxine combined with pyrimethamine and primaquine. This treatment also failed to eliminate the parasitaemia and fever in the following five days, when quinine was started, two g. daily for 10 days. The parasitaemia was cleared within five days and had not reappeared 33 days later.

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TABLE I. RESPONSE OF *P. FALCIPARUM* PARASITAEMIAS TO MULTIPLE DRUG REGIMENS.

| *Parasite Clearance* | *Sulphadimethoxine Primaquine Pyramethamine* | *Sulphormethoxine Primaquine Pyrimethamine* |
|---|---|---|
| Patients | 13 | 12* |
| Attacks | 15 | 14 |
| Parasite clearance days | | |
| Range | 1-4 | 1-4 |
| Average | 2·3 | 2·5 |
| Mode | 2 | 3 |

* Not included is one patient (F-2) who was not cleared after six days at which time quinine was started.

The most unusual case was a 15-month-old child who had eight attacks of *P. falciparum* malaria during a six-month period (Table III). Relapses occurred after seven separate treatments involving four different drug regimens, as follows: sulphadimethoxine combination, once; sulphormethoxine combination, twice; quinine, once; amodiaquine, thrice. The parasitaemias were cleared quickly after each treatment except for quinine.

Following the first treatment with sulphormethoxine, the malaria recurred 48 days later; after the subsequent treatments, the relapses were spaced between two and four weeks apart. The last treatment was with the sulphormethoxine combination. Sixty days later the blood was still negative indicating a cure. In spite of the malaria, the child gained 1·7kg. during the six months after the first attack.

## Discussion

Eleven of the patients had been treated previously once or more with chloroquine and/or amodiaquine. These drugs had failed to produce a radical cure. The infections which did not respond to, or relapsed after, the 4-aminoquinoline drugs were considered as resistant to those drugs.

Seven patients received the sulphormethoxine combination as the first treatment. The response appeared to be similar in those previously treated with the 4-aminoquinolines and in those not previously treated.

This indicates that the 4-aminoquinoline treatments apparently had no effect upon subsequent sulpha combination treatments and that there was no cross-resistance between these groups. Others also have found that some chloroquine-resistant *falciparum* infections were cured by a combination of sulphormethoxine and pyrimethamine: Chin *et al.* (1966) with Malayan and Thai strains; Laing in Malaya (1968a); Bartelloni *et al.* with Vietnam strains (1967); Harinasuta *et al.* in Thailand (1967). However, not all of the infections were radically cured by the suphormethoxine-pyrimethamine combination.

Similarly in Africa where chloroquine-resistant *P. falciparum* was not present but pyrimethamine-resistant strains were, Laing (1966, 1968b) got a high rate of cures using sulphormethoxine combined with pyrimethamine. The ability of this combination therapy to cure pyrimethamine-resistant strains, he believes, is due to a potentiating effect.

TABLE II. RELAPSES OF *P. FALCIPARUM* INFECTIONS AFTER TREATMENT WITH MULTIPLE DRUG REGIMENS. PATIENTS FOLLOWED UNTIL RELAPSE OR FOR 28 OR MORE DAYS.

| | *Sulphadimethoxine Pyrimethamine Primaquine* | *Sulphormethoxine Pyrimethamine Primaquine* |
|---|---|---|
| Patients | 12 | 6* |
| Malaria attacks: | 14 | 8 |
| Response: | | |
| Cured | 9 | 5 |
| Relapsed | 5 | 3 |
| Relapses: | | |
| Days after first day of treatment, range | 15 - 35 | 19 - 48 |

* Not included is one patient (F-2) who was not cleared after six days at which time quinine was started.

TABLE III. RESPONSE OF *P. FALCIPARUM* IN A CHILD TO FOUR DIFFERENT DRUG REGIMENS. WEIGHT 10·2 K. CASE NO. F-13.

| *Attack* | *Treatment* | *Days to parasite clearance* | *Days to relapse* |
|---|---|---|---|
| 1 | F | 3 | 48 |
| 2 | M | No data | 20 |
| 3 | Q | Not cleared until re-treated 15 days later | |
| 4 | A | 2 | 16 |
| 5 | A | 2 | 19 |
| 6 | A | 3 | 27 |
| 7 | F | 2 | 28 |
| 8 | F | 2 | Still negative 60 days later=cure? |

F=Sulphormethoxine, pyrimethamine & primaquine
M=Sulphadimethoxine, pyrimethamine & primaquine
Q=Quinine: 108 mg three times daily × 14 d=32 mg./kg./day
A=Amodiaquine—37·5 mg./kg. in three days.

Of particular interest was our case F-13 (Table III). Each of the seven times this child was treated with a synthetic drug, even with the 4-aminoquinolines, the parasites disappeared rapidly from the blood stream. There appeared to be no increase in resistance, as measured by the promptness of parasites removed, to subsequent treatments with the same drugs either 4-aminoquinolines or the sulpha combinations.

Equally puzzling is the failure of quinine to effect a cure or to clear the parasitaemia within 15 days. Usually quinine is the most reliable drug for radical cure of patients with drug-resistant *P. falciparum* malaria. During the past several years, 18 patients with *P. falciparum* malaria have been treated with quinine. This failure of quinine to cure is unique in our experience.


## Summary

In Panama, where *Plasmodium falciparum* resistant to 4-aminoquinoline drugs has been found recently, sulphadimethoxine or sulphormethoxine combined with pyrimethamine-primaquine were tested.

The parasitaemias responded rapidly to a combination of either of the two sulphonamide drugs combined with pyrimethamine and primaquine. However, more than one-third of the infections relapsed. In some cases there were multiple failures with these drugs.

There was no evidence of cross-resistance between the 4-aminoquinoline drugs and the sulphonamide combinations nor was there evidence that the response to the sulphonamide combinations was lessened by repeated treatments with the same drugs.

The failure to cure a child with seven separate treatments involving four different drugs is unexplained.



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