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SENSITIVITY OF PLASMODIUM FALCIPARUM TO ANTIMALARIAL DRUGS IN NANDI DISTRICT, KENYA[1]

by

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1. INTRODUCTION

The emergence of resistant Plasmodium falciparum in certain areas of the world has made it imperative that systems be established for the constant monitoring of P. falciparum sensitivity to drugs in use. In Kenya, studies to establish the sensitivity of P. falciparum to chloroquine, using the WHO standard in vivo and in vitro procedures, have been in progress for the past two years. In the course of these investigations the need arose to determine the efficacy of some antimalarial drugs which were frequently available in the pharmacies of both private and government hospitals. A study was therefore carried out in Nandi District using pyrimethamine, Fansidar (pyrimethamine + sulfadoxine) and chloroquine in the treatment of falciparum malaria.

2. MATERIALS AND METHODS

Semi-immune children aged 6 to 15 years, suffering from single infection with P. falciparum and with no evidence of having taken antimalarial drugs during the preceding month were selected for the study. All those who participated in the study had their urine tested for the presence of 4-aminoquinolines using the Dill Glazko test. The test was repeated on Days 1 and 3 of observation. Those positive and those who said that they had taken these drugs within the preceding month were excluded. No tests were made for the presence of sulfonamides but it is unlikely that any of the participants had taken these drugs.

The children to be studied were divided into four groups: Group 1 was treated with a single dose of 25 mg pyrimethamine; Group 2 received a single dose of Fansidar (500 mg sulfadoxine + 25 mg pyrimethamine); Group 3 received a single dose of 10 mg chloroquine base per kg body weight; and Group 4 received a dose of 25 mg chloroquine base per kg body weight, given over three days. Follow-up in each group was daily for seven days, starting from Day 0 (first day of treatment). Parasites were counted against 300 leukocytes and expressed in terms of the number of parasites per 1 microlitre of blood, taking 7000 leukocytes per microlitre as the normal average leukocyte count for Kenyans (personal observation).

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3. RESULTS

None of the 17 children who took pyrimethamine responded to treatment (see Table 1). Each patient was therefore treated with 25 mg chloroquine base per kg body weight whenever it became obvious that parasitaemia was rising. Of the 36 patients treated with Fansidar, 97.2% were cleared of their infections by Day 2, while only 54.2% of the 59 patients treated with 25 mg chloroquine base were cleared of their infections by Day 2 (see Table 2). However by Day 3 all the patients in both the Fansidar and 25 mg chloroquine treated groups were cleared of their infections. Finally, of the 33 patients treated with a single dose of 10 mg chloroquine base per kg body weight 63.6% had no detectable parasitaemia on Day 2 but on Day 3 the proportion showing no parasitaemia was 87.9%. Three people in this group were not cleared of their infections during the seven-day observation period although the parasite numbers were maintained at very low levels, and in one person parasitaemia reappeared on Day 7.

4. DISCUSSION

A large number of antimalarial drugs continue to find their way into the Kenyan market including private and government hospitals. However the continued use of some of these drugs, especially the dihydrofolate reductase inhibitors, either for prophylaxis or cure, cannot be justified in the light of the fact that resistance to them in East Africa has been known now for many years (Avery Jones, 1954; Clyde et al., 1958). A recent study in Kisumu (Dinh et al., personal communication) detected resistance in 14 out of 15 patients treated with 25 mg pyrimethamine. In the present study, 100% resistance to the same dose of pyrimethamine was detected in an area where Roberts (1956) had been able to control a malaria epidemic with the same dose of pyrimethamine 20 years earlier. The study results therefore seem to confirm that the P. falciparum populations of Nandi District, Kenya, are resistant to pyrimethamine although there is of course no real in vivo test for this drug. On the other hand, there is no conclusive evidence beyond the absence of RII and RIII responses that the same plasmodia were fully susceptible to chloroquine. The in vivo test was carried out for seven days only and, if the observations had been extended to 28 days under optimum conditions (avoidance of exposure to reinfection), breakthrough might have occurred.

Fansidar, which associates a dihydrofolate reductase inhibitor with a sulfonamide, is known to provide an effective treatment against forms of malaria resistant to chloroquine (Lewis & Ponnampalam, 1975; Pearlman et al., 1977; Doberstyn et al., 1976). However, this drug is already in use in Kenya despite the absence of resistance to chloroquine in infections among indigenous Kenyans (Masaba & Spencer, 1982; Spencer et al., 1982).

The present study has clearly demonstrated the efficacy of Fansidar and chloroquine in the treatment of malaria in Nandi District and this finding is in agreement with that of Dinh and co-workers in Kisumu. The current indiscriminate importation and use of a large collection of antimalarial drugs in Kenya is therefore not justifiable and should be discouraged. For the moment, chloroquine alone should be used for the treatment of malaria and Fansidar should be reserved for proven cases of resistance to chloroquine.

The fact that four out of 33 children remained positive after having received a single dose of 10 mg chloroquine/kg body weight must raise the issue of the selection of parasites with reduced sensitivity since the remaining parasites may be expected to survive the drug concentrations achieved with this dose. Large-scale use of the single dose regimen may therefore influence the drug sensitivity level of the P. falciparum population as a whole. This aspect should be considered in the policies of drug deployment.

5. SUMMARY

Studies were carried out in Nandi District, Kenya, to determine the sensitivity of P. falciparum to pyrimethamine, Fansidar and chloroquine. Pyrimethamine had no effect on P. falciparum, while chloroquine and Fansidar were very effective in clearing parasitaemia.

It is suggested that in the absence of confirmed resistance to chloroquine in infections among indigenous Kenyans, chloroquine should remain the drug of choice in the treatment of malaria, while Fansidar should be reserved for the treatment of proven cases of chloroquine resistance.

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RESUME

SENSIBILITE DE PLASMODIUM FALCIPARUM AUX MEDICAMENTS ANTIPALUDIQUES DANS LE DISTRICT DE NANDI, KENYA

Des études ont été effectuées dans le District de Nandi, Kenya, afin de déterminer la sensibilité de Plasmodium falciparum à la pyriméthamine, au Fansidar (500 mg sulfadoxine + 25 mg pyriméthamine) et à la chloroquine. La pyriméthamine s'est avérée n'avoir aucune action contre P. falciparum. Par contre, la chloroquine et le Fansidar se sont montrés très efficaces, faisant disparaître rapidement la parasitémie. Il semble qu'en l'absence de résistance confirmée à la chloroquine chez les indigènes du Kenya, la chloroquine devrait continuer à être considérée comme le médicament de choix dans le traitement du paludisme, tandis que le Fansidar devrait être réservé pour le traitement de cas de résistance confirmée à la chloroquine.

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TABLE 1. RESULTS OF TREATMENT OF P. FALCIPARUM MALARIA IN 17 CHILDREN WITH 25 mg PYRIMETHAMINE IN NANDI DISTRICT, KENYA

Code No.	Number of parasites per µl of blood							
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
28	3 675	677	460	630	2 870*	374	374	0
52	2 614	3 708	2 917	7 652	5 880*	9 847	327	0
80	1 307	5 250	4 200	1 947	7 256	12 647*	7 327	0
107	3 174	7 763	6 464	13 697	10 664*	3 882	0	0
108	4 434	3 466	5 337	3 117	2 170	2 126*	747	0
13A	10 547	67 537*	257	70	0	0	0	0
73B	2 770	40 183	10 850	94	1 144*	0	0	0
A105	490	560	794*	771	0	0	0	0
B36	1 074	2 170	1 237	2 609	1 540*	94	0	0
A45	1 378	3 524	7 323*	700	0	0	0	0
A97	1 149	2 357	9 595	11 675*	116	0	0	0
B52	589	164	117	159*	0	0	0	0
A24	1 186	6 347	23 590*	7 280	231	0	0	0
A98	3.174	1 820	3 244*	1 704	0	0	0	0
B37	251	140	2 730*	0	0	0	0	0
17	770	2 117*	0	0	0	0	0	0
47	607	1 494	1 214	794*	630	374	0	0

* Day of intervention with chloroquine.

TABLE 2. PARASITOLOGICAL FINDINGS IN CHILDREN AGED 6 TO 15 YEARS AFTER TREATMENT OF *P. FALCIPARUM* MALARIA WITH FANSIDAR (SULFADOXINE + PYRIMETHAMINE) AND CHLOROQUINE IN NANDI DISTRICT, KENYA

Day	Sulfadoxine 500 mg + pyrimethamine 25 mg (single dose in 36 children)		Chloroquine 25 mg/kg (over three days in 59 children)		Chloroquine 10 mg/kg (single dose in 33 children)	
	% positive	Parasite density No./µl (GM)	% positive	Parasite density No./µl (GM)	% positive	Parasite density No./µl (GM)
0	100.0	1 939	100.0	3 378	100.0	6 290
1	100.0	1 179	94.9	836	87.9	840
2	2.8	0.1	45.8	6.6	36.4	6.1
3	0	0	0	0	12.1	0.8
4	0	0	0	0	9.1	0.6
5	0	0	0	0	9.1	0.7
6	0	0	0	0	6.1	0.4
7	0	0	0	0	12.1	1.0

GM = geometric mean.