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THE EFFECT OF SULFAMONOMETHOXINE ON FALCIPARUM MALARIA

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Abstract: In this paper a report is made on 23 patients with falciparum malaria who were successfully treated with sulfamonomethoxine. Evidence has been presented: (1) that its effect on falciparum malaria is very remarkable, (2) that the intravenous administration is more effective than the oral one, (3) that also clinically chloroquine insensitive malaria responds to it, and (4) that no "relapse" is detected.

INTRODUCTION

As is well known, malaria is still widespread throughout East Africa, where a number of patients poorly respond to the chloroquine treatment (Pringle and Lane 1966, Himpoo and MacCallum 1967, Motala 1967), though it is generally accepted that there have been no substantiated cases of chloroquine resistance in Africa (Clyde 1966, Peters 1967, 1970, Wolfe and Huddleston 1969, Bruce-Chwatt 1970, Bruce-Chwatt and Roberts 1972). The exploitation of new antimalarial drugs has been a matter of serious concern. The introduction of sulfonamides as plasmocidal compounds has aroused a great deal of interest. The effects of sulfonamides such as sulfadiazine, sulformethoxine, sulfadimethoxine and sulfalene have been studied on falciparum malaria (Laing 1965, Baruffa 1966, Chin *et al.* 1966, Clyde 1967, Harinasuta *et al.* 1967, Martin and Arnold (1968). Yoshinaga *et al.* (1970) investigated the response of *P. berghei* against eight sulfonamides in mice and reported that sulfamonomethoxine was the most effective compound with the highest survival rates estimated in 30 and 50 days after the inoculation. They treated African patients from Embu area in Kenya with sulfamonomethoxine and noted its rapid effect on parasitemia. Schizontocidal action was confirmed in Laotian patients given oral medication of sulfamonomethoxine alone or in combination with pyrimethamine (Muto *et al.* 1971, Yamamoto *et al.* 1973). The present study was undertaken to evaluate the effect of sulfamonomethoxine on falciparum malaria in Rift Valley Province, Kenya.

MATERIALS AND METHODS

Sulfamonomethoxine was given either orally or intravenously to 23 patients with falciparum malaria admitted into Rift Valley Provincial Hospital in 1971. All of them were male Africans except one Japanese. Five cases out of 23 were

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clinically chloroquine insensitive. The blood was examined every day during the medication and further at regular intervals subsequently. Field staining method was used to demonstrate the plasmodia. The patients were divided into three groups:

Group 1, nine cases given oral medication
Group 2, nine cases given intravenous injection
Group 3, five chloroquine-insensitive cases treated either orally or intravenously

Dosage:

(1) Oral administration;
Sulfamonomethoxine, 2 g on the first day,
followed by 1 g daily for the next two to five days.

(2) Intravenous administration;
10 m*l* of 10 percent sulfamonomethoxine solution twice on the first day, repeated once a day for the next one to five days.

Results

Such symptoms as fever, chills, headache, lassitude, myalgia, joint pain and gastrointestinal disturbances have subsided in one or two days in all the nine cases of Group 1 treated with oral medication of sulfamonomethoxine. However, the time interval between initiation of therapy and disappearance of parasites from the blood of patients varies between one and eight days in Group 1 as indicated in Table 1. The nine cases of Group 2 including two patients with cerebral malaria given sulfamonomethoxine intravenously became asymptomatic within one day and parasite-free in one to three days after the start of treatment as shown in Table 2.

Table 1. Group 1, nine cases received oral medication of sulfamonomethoxine

Case	Sex	Age	Tribe	Total dose	Symptoms	Symptoms disappeared in	Parasite disappeared in	Effect	Complication
1	♂	25	Japanese	7 g	none	—	8 days	++	
2	♂	adult	Kalenjin	7 g	fever, headache, vomiting diarrhea	2 days	6 days	++	
3	♂	adult	Kisii	7 g	headache, abdominal pain	1 day	3 days	+++	
4	♂	adult	Kikuyu	5 g	none	—	2 days	+++	gout
5	♂	adult	Kikuyu	5 g	fever, headache, shaking chill, myalgia, diarrhea	1 day	1 day	+++	
6	♂	adult	Luo	5 g	headache, chill, myalgia	2 days	5 days	++	
7	♂	11	Kisii	4 g	fever, headache, vomiting, diarrhea	1 day	2 days	+++	
8	♂	adult	Luo	5 g	headache, myalgia	1 day	1 day	+++	
9	♂	adult	Luo	5 g	fever, headache	1 day	1 day	+++	

TABLE 2. Group 2, nine cases given sulfamonomethoxine intravenously

Case	Sex	Age	Tribe	Total dose, 10% 10 ml/ i. v.	Symptoms	Symptoms disappeared in	Parasite disappeared in	Effect	Complication
1	♂	15	Kalenjin	7 times	abdominal pain	1 day	1 day	±±	
2	♂	12	Lubya	7 times	fever, headache, myalgia, vomiting, abdominal pain	1 day	1 day	±±	
3	♂	adult	Kikuyu	7 times	fever, headache, coma	1 day	2 days	±±	cerebral malaria
4	♂	adult	Kikuyu	7 times	fever, headache, myalgia, chest pain, abdominal pain	1 day	1 day	±±	
5	♂	adult	Lubya	7 times	fever, myalgia	1 day	2 days	±±	hepato-splenomegaly
6	♂	adult	Luo	7 times	headache, myalgia	1 day	3 days	±±	
7	♂	15	Somali	3 times	fever, headache, myalgia, nausea, vomiting	1 day	1 day	±±	diabetes mellitus, pulmonary t.b.
8	♂	adult	Turkana	4 times	coma, convulsion	1 day	1 day	±±	cerebral malaria
9	♂	adult	Luo	4 times	fever, shaking chill, joint pain, vomiting, diarrhea	1 day	1 day	±±	

TABLE 3. Group 3, five chloroquine-insensitive cases treated with sulfamonomethoxine

Case	Sex	Age	Tribe	Total dose	Symptoms	Symptoms disappeared in	Parasite disappeared in	Effect	Complication
1	♂	2.5	Luo	7 times i.v.	none	—	2 days	±±	
2	♂	adult	Kikuyu	3 times i.v.	headache, myalgia, coma	2 days	1 day	±±	
3	♂	12	Lubya	7 times i.v.	fever, headache, myalgia, vomiting, abdominal pain	1 day	1 day	±±	
4	♂	14	Kikuyu	oral 7 g+7 g	fever, myalgia	1 day	3 days of the 2nd course	+	splenomegaly
5	♂	adult	Luo	oral 7 g	none	—	3 days	++	

It seems that falciparum malaria responds more promptly to the intravenous medication than to the oral one. Shown in Table 3 are the five cases of Group 3, in which even large doses of chloroquine had failed to decrease the number of plasmodia in their blood, treated either orally or parenterally with sulfamonomethoxine. In four cases of these patients insensitive to chloroquine the parasites disappeared from the blood in one to three days under sulfamonomethoxine treatment. The other one case, however, remained parasite-positive, though 7 g of the drug had been given orally in six days, and needed additional 4 g for the disappearance of plasmodium — the patient had to have the second course of oral administration. In all cases no side reaction due to sulfamonomethoxine was detected. Neither "clinical" nor "parasitemic relapse" has been found during the two months' follow-up investigations.

Discussion

Sulfonamides with or without dihydrofolate reductase inhibitors were tried on subjects with normal, chloroquine, multiple-resistant strains of falciparum malaria in Asia, South America and Africa (Peters 1970). Recrudescence after the treatment of *P. falciparum* with sulfadiazine was reported by DeGowin and Powell (1964) and Chin *et al.* (1966). Asexual parasitemia of *P. falciparum* was cleared with sulfalene and radical cure was recorded, though recrudescence was found in some patients (Baruffa 1966, Clyde 1967, Mazzoni 1967, Martin and Arnold 1968). Schizontocidal action of sulformethoxine against *P. falciparum* was reported (Laing 1964, 1965, 1968b, Clyde 1967). Sulformethoxine cured some of the non-immune and semi-immune subjects with falciparum malaria (Chin *et al.* 1966, Harinasuta *et al.* 1967). Radical cure was attained in the falciparum patients treated with the combinations of sulfonamides and dihydrofolate reductase inhibitors (DeGowin and Powell 1964, Chin *et al.* 1966, Bartelloni *et al.* 1967, Walker and Lopez-Antunano 1968, Laing 1968a). Against falciparum malaria the administration of sulfadiazine alone has not been recommended because of the frequent recrudescence. Long-acting sulfonamides appear to be more reliable. Sulfadimethoxine and sulfalene were reported to clear asexual parasitemia for a shorter time than does sulformethoxine (Clyde 1967). However, widely divergent results were obtained in the attempts to cure non-immunes with sulfalene (Baruffa 1966, Mazzoni 1967, Martin and Arnold 1968). It indicates that the sensitivities differ much among strains.

Sulfamonomethoxine, a close relative of sulformethoxine was found to be more potent than sulformethoxine and sulfadimethoxine against *P. berghei* in mice, and effective in both chloroquine-sensitive and allegedly chloroquine-resistant malaria in Embu area (Yoshinaga *et al.* 1970). In the present study the rationale of giving sulfamonomethoxine to the clinically chloroquine-insensitive patients is that there has been no substantial evidence of the chloroquine-resistant strains of *P. falciparum* showing a cross-resistance to sulfonamides. Chloroquine and sulfonamide are believed to act through entirely different mechanisms, so it is unlikely that the two compounds show cross-resistance with each other. Bishop and McConnachie (1948) reported that the proguanil-resistant strain of *P. gallinaceum* did not respond to sulfadiazine. It was recorded, however, that proguanil-resistant strain of *P. knowlesi*

responded normally to sulfadiazine, but exhibited high cross-resistance to pyrimethamine (Jaswant Singh *et al.* 1952). Pyrimethamine-resistant strains of *P. cynomolgi* (Jaswant Singh *et al.* 1953) and *P. knowlesi* (Jaswant Singh *et al.* 1954) were normally responsive to sulfadiazine but cross-resistant to proguanil. Excepting some compounds (e.g. methachloridine) which are not antagonized by para-aminobenzoic acid (Peters 1967), the mode of action of the sulfonamides seems to be competitive inhibition of para-aminobenzoic acid incorporation into folic acid (Marshall *et al.* 1942, Richardson *et al.* 1946, Thurston 1950). Inhibition of dihydrofolate reductase seems to be the basis for the chemotherapeutic action of pyrimethamine and biguanides (Ferone *et al.* 1969, Gutteridge and Trigg 1970). Pyrimethamine or biguanides and sulfonamides except above-mentioned some compounds act at different points in the same metabolic pathway — the folic acid cycle. This concept is also supported by the well-known fact that sulfadiazine potentiates the action of dihydrofolate reductase inhibitors, showing more than additive effect. Compounds acting through related, but distinctly different mechanisms in the same metabolic pathway show a low order of cross-resistance with each other: Strains which are highly resistant to cycloguanil and pyrimethamine usually show a low order of cross-resistance to most sulfonamides (Thompson and Werbel 1972). It is again the rationale of giving sulfamonomethoxine to the patients who might have been infected with the strains resistant to pyrimethamine or cycloguanil, which is possible in Africa.

It is generally accepted that sulfonamides should not be used alone in malaria because they are slow-acting, with narrow spectrum of activity and tend to induce the resistance of microorganisms to the drugs (WHO 1967). In the present study all symptoms disappeared within two days, but the average duration of asexual parasitemia was 3.2 days in Group 1: Factors contributing to this delay appear to include such aspects as the gastrointestinal symptoms, which some patients showed, probably having disturbed the absorption of the drug and a probable non-immune having joined this group. As shown in Table 1, a Japanese was free from symptoms, but it took 8 days to clear the parasitemia. It is very likely that the subject did not have antiplasmodial immune (McGregor 1971). The average duration of parasitemia was 1.4 days in Group 2, indicating that sulfamonomethoxine is rather rapid-acting if it is used intravenously. Even the patient in coma recovered very quickly. In Group 3 average duration of parasitemia was 1.3 days with the intravenous administration, manifesting its rapid effect. The Case 4 of this group given oral medication showed delayed clearance of parasitemia. This subject might have multiple-resistant strain. The fact that no recrudescence has been found in the two months' follow-up investigation seems to support that sulfamonomethoxine is one of the long acting sulfonamides worth clinical trials, especially in semi-immune subjects with or without dihydrofolate reductase inhibitors.

Untoward reactions to sulfonamides include hemolytic anemia related or unrelated to an erythrocytic deficiency of glucose-6-phosphate dehydrogenase, agranulocytosis, aplastic anemia, thrombocytopenia, urinary tract disturbances and Stevens-Johnson syndrome (Weinstein 1965). A 1.5% incidence of skin eruption was noted with sulformethoxine in North Africa (Bruce-Chwatt 1967). In the

present study, however, no side reaction attributable to sulfamonomethoxine has been detected, though these two sulfonamides are structurally related closely each other.

Extreme caution has to be exercised in intravenous administration of such hypotensive drugs as chloroquine and quinine to the patients in or verging on shock. It is often attempted to relieve the shock before treating with the hypotensive drugs. Immediate intravenous injection of sulfamonomethoxine appears to be worth trials in such emergency cases, because it is not a hypotensive compound.

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References

1) Bartelloni, P. J., Sheehy, T. W. and Tigertt, W. D. (1967): Combined therapy for chloroquine-resistant *Plasmodium falciparum* infection. Concurrent use of long-acting sulformethoxine and pyrimethamine, J. Amer. Med. Ass., 199 (3), 173–177
2) Baruffa, G. (1966): Clinical trials in *Plasmodium falciparum* malaria with a long-acting sulfonamide, Trans. Roy. Soc. Trop. Med. Hyg., 60 (2), 222–224
3) Bruce-Chwatt, L. J. (1967): Sulfonamides in malaria, Lancet, 2, 216
4) Bruce-Chwatt, L. J. and Roberts, J. M. D. (1972): Dissent on the alleged finding of chloroquine resistance in East Africa, Trans. Roy. Soc. Trop. Med. Hyg., 66 (2), 377–378
5) Clyde, D. F. (1966): Drug resistance of malaria parasites in Tanzania, East Afr. Med. J., 43 (10), 405–408
6) DeGowin, R. L. and Powell, R. D. (1964): Drug-resistant falciparum malaria, J. Lab. Clin. Med., 64 (5), 851–852
7) Gutteridge, W. E. and Trigg, P. I. (1970): Some studies on the effects of dihydrofolate reductase inhibitors, Trans. Roy. Soc. Trop. Med. Hyg., 64 (1), 12
8) Harinasuta, T., Viravan, C. and Reid, H. A. (1967): Sulformethoxine in chloroquine-resistant falciparum malaria in Thailand, Lancet, 1, 1117–1119
9) Jaswant Singh, Ray, A. P., Basu, P. C. and Nair, C. P. (1952): Acquired resistance to proguanil in *Plasmodium knowlesi*, Trans. Roy. Soc. Trop. Med. Hyg., 46 (6), 639–649
10) Jaswant Singh, Nair, C. P., Ray, A. P. and Misra, B. G. (1953): Development of resistance to pyrimethamine in *P. cynomolgi*, Indian J. Malar., 7 (4), 357–369
11) Jaswant Singh, Nair, C. P. and Ray, A. P. (1954): Studies on Nuri strain of *P. knowlesi*. V. Acquired resistance to pyrimethamine, Indian J. Malar., 8 (3), 187–195
12) Laing, A. B. G. (1964): Antimalarial effect of sulforthodimethoxine (Fanasil), Brit. Med. J., 2, 1439–1440
13) Laing, A. B. G. (1968b): Antimalarial effects of sulformethoxine, diaphenylsulfone and separate combinations of these with pyrimethamine. A review of preliminary investigations carried out in Tanzania, J. Trop. Med. Hyg., 71 (2), 27–35
14) Martin, D. C. and Arnold, J. D. (1968): The drug response of a normal and a multi-resistant strain of *P. falciparum* to sulfalene, Trans. Roy. Soc. Trop. Med. Hyg., 62 (6), 810–815
15) Mazzoni, P. (1967): Terapia della malaria acuta da *Plasmodium falciparum* con un sulfamidico

ritardo, Minerva Med. Roma., 58, 799–802
16) McGregor, I. A. (1971): Immunity to plasmodial infections; consideration of factors relevant to malaria in man, International review of tropical medicine (Woodruff, A. W. and Lincicome, D. R., eds.), Vol. 4, 1–52, Academic Press, New York and London
17) Muto, T., Ebisawa, I. and Mitsui, G. (1971): Malaria at the Nam Ngum Dam construction site in Laos, (Therapeutic effects of combined folic inhibitors and other drugs), (in Japanese), Nettai, 5 (4), 204–213
18) Peters, W. (1967): A review of recent studies on chemotherapy and drug resistance in malaria parasites of birds and animals, Trop. Dis. Bull., 64 (11), 1145–1175
19) Peters, W. (1969): Drug resistance in malaria—a perspective, Trans. Roy. Soc. Trop. Med. Hyg., 63 (1), 25–40
20) Peters, W. (1970): Chemotherapy and drug resistance of malaria, 470–473, Academic Press, London and New York
21) Pringle, G. and Lane, F. C. T. (1966): An apparent decline in the efficacy of small doses of chloroquine in suppressing malaria parasitemias in semi-immune African schoolchildren, East Afr. Med. J., 43 (12), 575–578
22) Thompson, P. E. and Werbel, L. M. (1972): Antimalarial agents. Chemistry and pharmacology, 271–274, Academic Press, New York and London
23) Walker, A. J. and Lopez-Antuñano, F. J. (1968): Response to drugs of South American strains of *Plasmodium falciparum*, Trans. Roy. Soc. Trop. Med. Hyg., 62 (5), 654–667
24) Weinstein, L. (1965): Chemotherapy of microbial diseases. Sulfonamides, The pharmacological basis of therapeutics (Goodman, L. S. and Gilman, A., eds.), 3rd ed., 1144–1170, Macmillan, New York
25) Yamamoto, T., Amano, H., Yamanaka, T., Iwamoto, H., Aihara, M., Okada, M., Ono, Y. and Shibazaki, S. (1973): Effect of sulfamonomethoxine, chloroquine and pyrimethamine upon *Plasmodium falciparum* and *vivax* in Laos, (in Japanese), Nettai 7 (3, 4), 153–163
26) Yoshinaga, T., Tsutsumi, Y., Tsunoda, K. and Yamamura, Y. (1970): Studies on the antimalarial property of 4-methoxy-6-sulfanilamido-pyrimidine monohydrate (sulfamonomethoxine; DJ–1550) and on its effect on the chloroquine-resistant malaria, Arzneim.–Forsch., 20 (9), 1206–1210

Sulfamonomethoxine の熱帯熱マラリアに対する効果について

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著者らは1971年ケニア，ナクルーの Rift Valley Provincial Hospital に入院した熱帯熱マラリア患者23例を対象として Sulfamonomethoxine を経口及び静注により投与しマラリア原虫に対する効果を検討した。

その結果全例に原虫の消失がみられた。原虫陰転までの期間は経口法に比べ静注法が短い。

又本剤はクロロキン不感受性株にもすぐれた効果を示した。サルファ剤の schizontocidal effect について文献的考察を試みた。

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