EFFECTS OF SULFAMONOMETHOXINE, CHLOROQUINE AND PYRIMETHAMINE AGAINST PLASMODIUM FALCIPARUM AND PLASMODIUM VIVAX IN THE KINGDOM OF LAOS

With special reference to evaluation of antimalarial efficacy of sulfamonomethoxine

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Abstract: Exclusive therapy with sulfamonomethoxine, exclusive therapy with chloroquine, and the therapy with the combination of sulfamonomethoxine and pyrimethamine have individually been applied to 118 patients with malaria in Laos, and the effects were comparatively evaluated on the basis of quantitative progress in asexual parasitemia. The results are summarized as follows: 1) The presence of chloroquine-resistant type of malaria was suspected. 2) It was confirmed that sulfamonomethoxine has therapeutic efficacy comparable to that of chloroquine. 3) The therapeutic efficacy of sulfamonomethoxine was of a delayed type. 4) The combination of sulfamonomethoxine and pyrimethamine showed 100% effectiveness in the disappearance of parasitemia on blood films. 5) The following method was established on the ground of the above findings for the prophylaxis and therapy of malaria: For prophylaxis of malaria, 500 mg of sulfamonomethoxine should be administered twice a week, provided that the MP-therapy is at any time available. For the treatment of malaria, exclusive therapy with sulfamonomethoxine should be used as the first choice, and the progress in the number of asexual parasitemia should be observed for at least one week while this therapy is being applied. Until the number of asexual parasitemia increases or is found to remain unexpelled even one week after its administration, no other therapy such as chloroquine or the combination of sulfamonomethoxine and pyrimethamine should be applied.

Even today, malaria is still one of the tropical diseases that require much attention. Since 1966 we have continued the clinical service activities at Brazzaville, Congo, Africa. Since 1970 visiting clinic services have also been carried out by our medical team in the Kingdom of Laos, Southeast Asia.51)

Quinoline derivatives have been the essential drugs for the therapy of malaria at the present time.182145) In fact, our therapy and prophylaxis against malaria have depended mainly on quinoline derivatives so far. However, in view of acci-

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dental incidents of malaria among our members and of the hepatic disturbances attributable to their administration, routine administration of chloroquine against malaria should be re-evaluated. In addition, from the observation of the patients we treated in tropical areas, it may be assumed that there exists chloroquine-resistant malaria. Two cases of chloroquine-resistant *Plasmodium falciparum* infection in Colombia were reported in 1961, followed by many reports on the similar cases in Thailand, Cambodia, Malaysia, Vietnam, Singapore, the Philippines, and Laos. Some of them were found to be also resistant to other antimalarials, and some others were also found to have reduced their response to quinine.

Malaria was almost entirely eliminated in Japan for a time being after the Second World War, but, as the number of Japanese travellers abroad increased, the number of malarial patients also increased, and even the death due to this disease have been reported. We have had a case with *Plasmodium ovale* Stephens brought back from Brazzaville, Congo.

The available antimalarials besides quinoline derivatives are various sulfonamides as the p-aminobenzoic acid antagonists, pyrimethamine, chloroguanide and cycloguanil pamoate as the folic acid reductase inhibitor and a new drug, called colchicine.

In our clinical service activities in Laos, observations were made on the effect of three methods of treatment: exclusive use of chloroquine, exclusive use of sulfamonomethoxine, and combination of sulfamonomethoxine and pyrimethamine on *Plasmodium falciparum* and *Plasmodium vivax*. The therapeutic effects of these three agents have been compared and evaluated with the reduction rate of asexual parasitemia as an indication. Based on these results, we will discuss the prophylaxis and therapy against malaria.

**Materials and Methods**

**Materials:**

Patients in Ban Keun village and refugee camps in the neighboring villages in Laos were the subject of this study. The number of patients we treated were 118 in total. They were diagnosed by means of thick or thin blood films. 118 cases of malaria consisting of 79 *Plasmodium falciparum* and 39 *Plasmodium vivax*, of which 3 cases were reinfected and 2 cases were superinfected. Of these 118 patients, 57 cases were followed-up using thick or thin blood film tests to indicate asexual parasitemia.

**Drug Administrations:**

The patients were divided into three groups in order to compare and to evaluate the effectiveness of the treatment regimens.

**Drugs Used in Each Group Were as Follows:**

1. Exclusive sulfamonomethoxine therapy (M group)
The first day: 40 mg/kg of body weight
The second day: 20 mg/kg of body weight
The third day: 20 mg/kg of body weight

2. Exclusive chloroquine therapy (C group)
   Chloroquine 1,500 mg therapy
   The first day: 600 mg
   Six hours later: 300 mg
   The second day: 300 mg
   The third day: 300 mg
   in accordance with the WHO method based on a dose of 1,500 mg.

3. Combinations of sulphanomethoxine and pyrimethamine therapy (MP group)
   1 mg of pyrimethamine and 20 mg of sulphanomethoxine per kg of body weight.
   This combination was given at the same time.

RESULTS

As the result of treatment, the disappearance ratio of asexual parasitemia was 55% in the M-group, 54% in the C-group and 100% in the MP-group (Tables 1 and 2).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of cases</th>
<th>Number of cases</th>
<th>ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-group</td>
<td>22</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>C-group</td>
<td>13</td>
<td>7</td>
<td>54</td>
</tr>
<tr>
<td>MP-group</td>
<td>22</td>
<td>22</td>
<td>100</td>
</tr>
</tbody>
</table>

M — sulphanomethoxine,  C — chloroquine
MP — sulphanomethoxine + pyrimethamine
* Number of disappearance of asexual parasitemia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Type of malaria</th>
<th>Number of cases</th>
<th>Number of cases</th>
<th>ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-group</td>
<td><em>Plasmodium falciparum</em></td>
<td>11</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td><em>Plasmodium vivax</em></td>
<td>7</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>C-group</td>
<td><em>Plasmodium falciparum</em></td>
<td>7</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td><em>Plasmodium vivax</em></td>
<td>5</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>MP-group</td>
<td><em>Plasmodium falciparum</em></td>
<td>13</td>
<td>13</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td><em>Plasmodium vivax</em></td>
<td>8</td>
<td>8</td>
<td>100</td>
</tr>
</tbody>
</table>

* Number of disappearance of asexual parasitemia

However, it should be noted that the blood examinations were occasionally carried out on separate days due to the difficult travelling conditions of the medical
The relationship between the dates of examination after treatment and the results concerning the disappearance of asexual parasitemia is shown in Table 3.

Table 3 The effect of treatment upon disappearance of asexual parasitemia

<table>
<thead>
<tr>
<th>Time after treatment</th>
<th>M-group</th>
<th>C-group</th>
<th>MP-group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of tested cases</td>
<td>Number of disappearance cases</td>
<td>*</td>
</tr>
<tr>
<td>2nd day</td>
<td>6</td>
<td>5</td>
<td>4 2 4 4</td>
</tr>
<tr>
<td>3rd day</td>
<td>14</td>
<td>1</td>
<td>1 1 1 1</td>
</tr>
<tr>
<td>4th day</td>
<td>2</td>
<td>2</td>
<td>2 2 2 2</td>
</tr>
<tr>
<td>5th day</td>
<td>4</td>
<td>3</td>
<td>2 11 10</td>
</tr>
<tr>
<td>6th day</td>
<td>2</td>
<td>1</td>
<td>1 5 5 5</td>
</tr>
<tr>
<td>7th day</td>
<td>4</td>
<td>1</td>
<td>1 3 2 2</td>
</tr>
<tr>
<td>2 weeks</td>
<td>1</td>
<td>1</td>
<td>1 4 5 5</td>
</tr>
<tr>
<td>3 weeks</td>
<td>1</td>
<td>1</td>
<td>1 4 5 5</td>
</tr>
<tr>
<td>4 weeks</td>
<td>1</td>
<td>1</td>
<td>1 4 5 5</td>
</tr>
<tr>
<td>5 weeks</td>
<td>1</td>
<td>1</td>
<td>1 4 5 5</td>
</tr>
</tbody>
</table>

* Number of tested cases
** Number of disappearance cases

Among those M-group patients who were treated with sulfamonometoxine alone, 20 cases were followed-up on the second or third day after the treatment, only 5 cases turned to negative. Whereas, of the 6 cases which were followed-up on the 6th or 7th day, 5 cases were found to have turned to negative. One case did not indicate negative reaction even in the 4th week after medication.

In the C-group, neither at early stage (third day) nor about two weeks after the treatment, did anyone turn to negative.

In the MP-group, asexual parasitemia in blood film of all the patients except 2 disappeared in the subsequent examination, either immediately after or 1 to 3 weeks after the medication.

Table 4 shows the results of the changes in the number of asexual parasitemia on observation day after the treatment.

In the M-group, 21 patients were followed-up on the 2nd, 3rd or 4th day after the therapy. Of these, 6 cases showed no asexual parasitemia detected in the blood film. In 9 cases, more than 80% reduction in the number of asexual parasitemia was seen. Four cases showed a reduction of more than 50% in the number of asexual parasitemia. Only two patients showed no change in the number of asexual parasitemia even during administration of this drug.

Of the 12 patients whose turning to negative was confirmed, 7 cases were found with *Plasmodium falciparum* and 3 cases with *Plasmodium vivax*. Four of these with *Plasmodium falciparum* turned to negative on the third day, while another on the 4th day and the other two on the 7th day. The two cases which turned to negative on
the 7th day were both checked during the treatments. One of them showed a reduction of 66% on the 3rd day, and the other showed 22% on the 5th day. Of the three cases with *Plasmodium vivax*, one turned into negative on the third day, while the other two turned into negative on the 6th day. Of the latter two, one showed a reduction of 80% and the other 87% on the third day.

From the above-mentioned results, it may be claimed that although the disappearance ratio of asexual parasitemia of the M-group amounted to only 50% at our post-medication check, sulfamonomethoxine even when administered alone can provide good therapeutic effect against *Plasmodium falciparum* and *Plasmodium vivax*.

Of the 13 patients who underwent chloroquine alone (C-group), 7 cases turned to negative.

Of the 6 cases which showed no negative turning, 3 were checked at the end of the 1st, 2nd and 3rd week respectively, showing more than 80% reduction. (explored on the end of the 1st, 2nd, and 3rd week, respectively)
their clinical symptoms, they were suspected to be of the chloroquine-resistant type of malaria. These 6 cases were switched to either the M-group or the MP-group but, unfortunately, no further followed-up has been made.

Of the 22 cases of the MP-group, 20 cases showed disappearance of asexual parasitemia at the time of the post-medication check. Of the two cases which showed no negative turning at the primary post-medication test, one showed improvement in his clinical symptoms at the end of the first week after the medication, but showed increase in asexual parasitemia in his blood specimens. However, at the end of the third week after the medication, with no additional medication, the asexual parasitemia disappeared. One patient was febrile at the end of the third week, and was eventually found to have asexual parasitemia. Re-medication was then started and the asexual parasitemia disappeared two weeks later (at the end of the 5th week after the initial medication).

**DISCUSSION**

Quinoline derivatives have so far been used widely against malaria as a remedy for both its prophylaxis and therapy. However, since the chloroquine-resistant malaria was reported in many areas in recent years, it was claimed that the prophylactic and therapeutic methods against malaria should be re-evaluated. It has been known that sulfonamides is effective for the therapy against malaria since Coggeshall reported on sulfadiazine in 1941. However, their practical use was rare in view of the outstanding efficacy of quinoline against the disease. Later, the effects of sulfamethoxine, sulfadimethoxine, sulfamethoxypyridazine, sulfalene, and many other sulfonamides were reported.

Especially, concerning the sulfones, diaphenylsulfone (D. D. S.) became the object of particular attention and its schizontocidal effect was reported. Furthermore, it was reported that diformyl diamino diphenyl sulfone (D. F. D.) was even more effective. Sulfonamides appear to be effective and the longer acting drugs appear to be more effective, probably because of the maintenance of longer and more constant antagonism to para-aminobenzoic acid. Particularly noted is the fact that the efficacy of sulformethoxine with 100 to 200 hours’ half life should be attended to in the future. Yoshinaga reported in 1970 that sulfamonomethoxine was effective against *Plasmodium falciparum* in Kenya.

In the course of prophylaxis and therapy against malaria within the staff of our overseas medical service team, we used to apply mainly chloroquine, but had been disturbed by the hepatic disorders due to chloroquine. Amano et al., our colleagues, reported that malaria broke out in the hiatus of chloroquine administration which were to be discontinued because of emerging hepatic disturbances after administration.

Further, the application of chloroquine which has long been used in the orthopedic field has come to be avoided due to the recent upheaval of the iatrogenic diseases caused by excessive medication like the SMON disease which is ascribed to the long-term administration of chinoform.

From these facts, we feel that the use of chloroquine as a prophylactic drug against
malaria should be re-examined. Although sulfonamides can not always be free from side effects, no particularly notable reports have been published so far on its side effects even though it has been daily applied over several years as one of the combined chemotherapy against pulmonary tuberculosis. As clearly realized by our present study, it can be claimed that the exclusive administration of sulfamonomethoxine has sufficient efficacy, not inferior to that of chloroquine, against malaria. Our studies indicate that the efficacy of sulfamonomethoxine is better than that of chloroquine. From the above-mentioned findings it is our belief that sulfamonomethoxine is preferable to chloroquine for the prophylaxis and therapy of malaria in the present practice.

Pyrimethamine, chloroguanide, cycloguanil pamoate, and trimethoprim as folic acid reductase inhibitor were introduced to the clinical use against malaria. It has been, however, reported that these new antimalarials are more toxic to human bodies than sulfonamides according to their actions to cause megaloblastic changes in the bone marrow and to invite anemia due to their inhibitory effects against folic reduction. Of these antimalarials, pyrimethamine was developed in 1948 by G. H. Hitchings, followed by many investigations concerning this drug. However it should be noted that pyrimethamine is prone to develop resistance. It has been reported that this agent was effective against both Plasmodium falciparum and Plasmodium vivax, but the amount of the therapeutic dose of an antimalarial varies depending on the strains of Plasmodium falciparum, and that large parasitemias and large doses of this agent will develop a high degree of resistance, much faster than the method of repeated exposure to small doses. Since chloroquine resistant malaria has acquired cross resistance, antimalarials with many modes of different association have been re-examined. First of all, the combination of sulfadiazine with pyrimethamine was studied, followed by those of chloroquine with quinine of mepacrine, but their effects were found to be insufficient. The combination of one of sulfonamides or sulfones with one of the folic reductase inhibitors has been shown to produce a true synergism as the folic acid pathway was attacked at two different places. Various ways of combination were tried, such as sulfone and pyrimethamine, sulfalene and trimethoprim, sulfamethoxazole and trimethoprim, and D. F. D. and trimethoprim. Among them, the combination of sulfomethoxine and pyrimethamine has attracted the greatest interest, and a large number of reports have been published. Because of the difficulty in obtaining large quantities of Fansidar (the combination of sulfomethoxine and pyrimethamine), the combination of sulfamonomethoxine and pyrimethamine (MP-group) was adopted in our present study. As reported in this paper, its efficacy amounted to 100% in the disappearance of parasitemia in blood film. This is an excellent result. The outstanding efficacy was also confirmed in a refugee camp. Our second team rendered their treatment to almost all inhabitants of the camp against malaria which was rampant at that time, and ten months later, the third team could hardly find any one still affected by malaria. However, several points have yet to be re-examined before applying the remedy further to more extensive uses.

Firstly, it should be pointed out, as discussed from literature, that pyrimethamine is characterized by its likelihood to acquire resistance. Secondary, the fact that this drug achieved 100% efficacy may suggest that there might have been excessive ad-
ministration of this medicine to malaria. In fact, WHO also admitted that further studies would be needed in determination of its final dose against the disease. One of the problems to be mentioned here is that the single dose of 1,000 mg/50 kg of sulfamonomethoxine and 50 mg/50 kg of pyrimethamine (2 tablets of MP) is sufficient for attaining 100% efficacy and that a dose of 500 mg of sulfamonomethoxine and 25 mg of pyrimethamine (a tablet of MP) is needed once a week for prophylaxis against malaria. Taking into consideration the above-mentioned points, it may be claimed at least that the particular combination would be highly effective if it is applied at one swoop in accordance with a careful plan to eradicate malaria in a district. It should be, however, pointed out that, in view of this outstanding efficacy, its fragmental or insufficient use only to stop symptoms should be strictly restricted.

References

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ラオスに於けるマラリアに対する Sulfamonomethoxine, Chloroquine 及び Pyrimethamine の治療成績の比較検討

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相原 雅典・岡田 雅幸・小野 喜雄・柴崎 定男2

ラオスに於ける118例のマラリア患者に対して、Sulfamonomethoxine 単独療法、Chloroquine 単独療法および Sulfamonomethoxine と Pyrimethamine の合剤による療法を行い、その効果を asexual parasitemia の量的推移を基本にして比較検討して以下に推論を得た。1）Chloroquine 耐性のマラリアの存在が推察された。2）Sulfamonomethoxine は Chloroquine に劣らない治療効果があることが確認された。3）Sulfamonomethoxine の治療効果は速効性であるように考えられた。4）Sulfamonomethoxine と Pyrimethamine の合剤は、血液塗抹標本中の原虫消失に100％の治療効果を示した。5）以上の諸成績をもとにして、マラリアの予防と治療に関して以下的方法が確立された。マラリアの予防に関し

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