CLINICAL TRIAL OF TRIMETHOPRIM-SULFAMETHOXAZOLE IN THE TREATMENT OF VIVAX, OVALE AND FALCIPARUM MALARIA¹

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Abstract: A compound of trimethoprim (TMP) and sulfamethoxazole (SMZ) was effective in the treatment of vivax, ovale and falciparum malaria. Two patients with vivax malaria received 16 mg TMP/80 mg SMZ/kg body weight in 3 divided doses daily for 3 days. A patient with ovale malaria received 10 mg TMP/50 mg SMZ/kg body weight in 4 divided doses daily for 4 days. These doses were followed by 15 mg primaquine daily for 2 weeks. A patient with falciparum malaria received 16 mg TMP/80 mg SMZ/kg body weight in 3 divided doses daily for 3 days. In all patients, radical cures were achieved; neither relapse nor recrudescence has occurred. Trimethoprim-sulfamethoxazole succeeded in causing rapid clearance of asexual-parasites from peripheral blood of the patients and producing rapid defervescence. No symptomatic adverse reactions to TMP-SMZ were experienced.

INTRODUCTION

In Japan, indigenous malaria (falciparum, vivax and malarial malaria) was eradicated by the 1960s. However, the problem of malaria imported from other parts of the world has become more serious since 1970. During 1972–1981, 697 imported cases of malaria, including 15 deaths in falciparum malaria, were reported in Japan (Ohtomo and Hioki, 1985). Most of the standard anti-malarial drugs including amodiaquine, chloroquine, proguanil, primaquine and pyrimethamine are not commercially available in Japan. Physicians are anticipating anti-malarial drugs which can be easily obtained in Japan.

The effectiveness of trimethoprim-sulfamethoxazole (TMP-SMZ), which is commercially available in Japan, in the treatment of falciparum and vivax malaria has been reported. However, no study has been done on the efficacy of TMP-SMZ in treating ovale malaria. The present paper describes satisfactory therapeutic results of this compound in the treatment of symptomatic vivax, ovale and falciparum malaria.

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METHODS

The cases in the present study include 2 vivax malaria patients (Case 1 and 2), one ovale malaria patient (3) and one falciparum malaria patient (4). All patients were hospitalized and examined as follows: 1) Thin films of peripheral blood were examined for identification of species and stages of malarial parasite and for parasite counts. The number of parasites/200 white blood cells were converted into the number of parasites per μl (parasite count) by calculations based on white blood cell counts taken on the same days. 2) Axillary temperature was taken. 3) Routine hemograms were done, recording the number of red blood cells/ μl (RBC), the ratio of reticulocyte to whole RBC (Retics), hemoglobin amount (Hb), hematocrit (Ht), the number of platelets/ μl (Plts), the number of white blood cells/ μl (WBC) and differential white blood cells count. 4) Liver function tests and other routine biochemistry were performed.

All patients were treated with an oral TMP-SMZ compound (Baktar®, Shionogi & Co., LTD., Osaka, Japan). One tablet contained 80 mg TMP and 400 mg SMZ. Cases 1, 2 and 4 were administered 16 mg TMP/80 mg SMZ/kg body weight (Bw) in 3 divided doses daily for 3 days. Case 3 was administered 10 mg TMP/50 mg SMZ/kg Bw in 4 divided doses daily for 4 days. The casualties totaled 12×3 tablets in Case 1 (Bw=60 kg), 8×3 tablets in Case 2 (Bw=40 kg), 9×4 tablets in Case 3 (Bw=72 kg) and 14×3 tablets in Case 4 (Bw=70 kg). In addition, Cases 1, 2 and 3 were administered 15 mg primaquine daily for 14 days following the TMP-SMZ doses.

Sera from Cases 2 and 4 were analyzed for the presence of antibodies to erythrocytic stages of *Plasmodium vivax* and *P. falciparum* by an indirect fluorescent antibody technique (IFA).

CASE STUDY

Figures 1–4 are the courses of treatment showing body temperature, asexual-parasite counts and sexual-parasitemia of the patients.

Case 1 (Vivax malaria with low parasitemia) (Figure 1)

Present illness: On 2 September 1981, a 33-year-old Japanese male developed chills and fever and visited the Department of Medical Zoology, Kyoto Prefectural University of Medicine for consultation. Immediate blood examination revealed the presence of *P. vivax*, and parasite count was recorded as 675 parasites/ μl of blood with 89% trophozoites and 11% schizonts. On 3 September he was hospitalized. Tertian-type high fever attack was found on 4 (39.7°C) and 6 (39.8°C) September and another high parasite count (675/ μl) was recorded on 5 September. A hemogram on 4 September recorded Hb of 14.3 g/dl; Ht 45.8%; RBC 461×10^4 ; WBC 5,000 with 40% neutrophils, 17% lymphocytes, 9% monocytes, 33% eosinophils and 1% basophils. On 7 September, Hb was 12.7 g/dl, Ht 40.0%, RBC 401×10^4 and WBC 4,100. A physical examination showed a slight hepato-splenomegaly.

History: The patient suffered his first attack of malaria in Zaire in March 1975. He had been there since September 1974 doing anthropological investigations. Until February 1975, one month prior to the onset of the first attack, he had continued weekly chloroquine. This attack was terminated with chloroquine (dose unknown). He returned to Japan in September 1975. During his next visit to Zaire from March 1978 to March 1979, the patient suffered another malarial attack, which subsided after treatment in a hospital. He made a third visit to

Vivax malaria

(33Y, MALE)

Figure 1 Course of temperature, asexual-parasite count and sexual-parasitemia in the patient, a 33-year-old Japanese male with vivax malaria (Case 1). The patient was given an oral compound of trimethoprim-sulfamethoxazole (ST) at a dosage of 16 mg TMP/80 mg SMZ/kg Bw in 3 divided doses daily for 3 days, followed by 15 mg primaquine daily for 14 days.

Zaire, from August 1979 to February 1980. During this period no further attack was experienced. On 5 June 1980, 3 months after his return from Zaire to Japan, he developed fever and chills and took chloroquine phosphate Resochin® (dose unknown), without successive primaquine administration. After that the patient had no suggestion of malaria for 15 months until the present episode of illness.

Treatment: On 9 September 1981, he was started on 12 oral tablets of TMP-SMZ in 3 divided doses daily (16 mg TMP/80 mg SMZ/kg Bw/a day) for 3 days. Beginning 13 September, 15 mg primaquine was administered daily for 14 days.

An examination, done just prior to this treatment, revealed a parasite count of 82/ μ l of blood with 100% asexual-parasite. Asexual-parasite count became 0/ μ l within 24 hours after the first dose was given and remained at 0/ μ l after this time. Sexual-parasite count was 0/ μ l 52 hours after the beginning of treatment. Since then no parasites were observed on thin films. The patient's temperature was normal since 7 September. A hemogram on 11 September recorded Hb of 13.4 g/dl; Ht 38.6%; RBC 421×10^4 ; WBC 5,200 with 47% neutrophils, 30% lymphocytes, 3% monocytes, 19% eosinophils and 1% basophils. The results of the following examinations on 21, 24, 28, 29 September were within normal range, except for eosinophilia. Upon later review of the smears, microfilaria was detected and identified *Dipetalonema perstans* as previously reported (Yoshida *et al.*, 1983). Eosinophilia recorded throughout the period examined might be due to *D. perstans* infection. No symptomatic adverse reactions to TMP-SMZ were observed. To date, no relapse of malaria has been experienced.

Case 2 (Vivax malaria with high parasitemia) (Figure 2)

Present illness: On 7 June 1984, a 37-year-old Japanese nurse developed chills and fever.

Figure 2 Course of temperature, asexual-parasite count and sexual-parasitemia in the patient, a 37-year-old Japanese female with vivax malaria (Case 2). The patient was given an oral compound of trimethoprim-sulfamethoxazole (ST) at a dosage of 16 mg TMP/80 mg SMZ/kg Bw in 3 divided doses daily for 3 days, followed by 15 mg primaquine daily for 14 days.

On 8 June she made a blood smear and found a malaria parasite. On 9 June she was admitted to Kyoto Municipal Hospital and the malarial parasite was identified as *P. vivax*. There were 688 parasites/ μ L on 8 June and 1,075/ μ L on 9 June; asexual-parasites were 97% and 98% of total parasites respectively. A hemogram on 9 June recorded Hb of 13.6 g/dL; Ht 40.1%; RBC 427×10^4 ; WBC 4,300 with 26% neutrophils, 63% lymphocytes, 10% monocytes and 1% basophils. Liver function tests and other routine biochemistry were all normal. The highest parasite count was 25,870/ μ L with 93.9% trophozoites, 0.5% schizonts and 5.6% gametocytes on 12 June. Intermittent tertian paroxysms peaking at the night on 8, 10 and 12 June were marked, although on 13 and 14 June paroxysms were irregular. The highest temperature recorded was 40.2 $^{\circ}$ C on 8 June.

History: The patient had traveled in Thailand, Malaysia, Nepal, India and Australia 4 times in 10 years; October 1975 to November 1976, February 1978 to November 1979, February 1980 to July 1980 and October 1981 to September 1983. She took a prophylactic drug against malaria during the first trip only. She suffered her first attack of malaria in India in May 1980. This attack subsided after taking a course of amodiaquine (Camoquin®, dose unknown). In August 1980, one month after she returned to Japan, a relapse was experienced, which was terminated with amodiaquine (Camoquin®, dose unknown). This was not followed by primaquine. In November 1980 she had a normal delivery of a girl. Until 7 June 1984, no relapse occurred.

Treatment: From 14 June 1984 in the present therapeutic schedule, she was given 8 oral tablets of TMP-SMZ in 3 divided doses daily (16 mg TMP/80 mg SMZ/kg Bw/a day) for 3 days followed by 15 mg primaquine daily for 14 consecutive days.

On 14 June an examination done just prior to this treatment, revealed a parasite count of $12,765/\mu\text{l}$ with 68% trophozoites, 7.9% schizonts and 24.0% gametocytes. A hemogram on this day recorded Ht 35.0%, RBC 356×10^4 and WBC 3,000. Asexual-parasite count became $0/\mu\text{l}$ within 48 hours after the beginning of treatment. Thereafter the temperature was normal although a slight fever (37.7°C) on 16 June was experienced. A hemogram on 16 June recorded Hb of 9.8 g/dl; Ht 31.0%; RBC 312×10^4 ; Retics 1.3%; Plts 66×10^3 ; WBC 6,700 with 57% neutrophils, 31% lymphocytes, 11% monocytes and 1% eosinophils. On 19 June the recordings were Ht 28.0%, RBC 308×10^4 and WBC 4,900. Since then, the Hb and Ht levels gradually returned to normal over a period of 2 months. The number of red blood cells/ μl was 341×10^4 on 26 June, 328×10^4 on 2 July, 397×10^4 on 15 August and 438×10^4 on 19 September. Hematocrit was 30.5%, 32.0%, 38.0% and 41.0% respectively. Hemoglobin amount was 10.4 g/dl on 26 June, 12.7 g/dl on 15 August, and 13.6 g/dl on 19 September. Reticulocytes was 8.0% and Plts was 291×10^3 on 26 June. Liver function tests and other routine biochemistry on 26 June were all normal. No symptomatic adverse reactions to TMP-SMZ were observed. To date, no relapse has been experienced.

Serum was analyzed for antibodies against malarial parasites by the IFA test; the serum dilution end-points were 1:256 against *P. vivax* and 1:64 against *P. falciparum* on 12 June and 2 July. On 15 August these were 1:64 against *P. vivax* and 1:16 against *P. falciparum*.

Case 3 (Ovale malaria) (Figure 3)

Present illness: A 29-year-old Japanese male developed fever and chills on 29 May and 2 June 1983, 3 months after his return to Japan from Kenya. On 2 June he was admitted to Kyoto Municipal Hospital when he was temporarily diagnosed as vivax malaria. However, upon later

Figure 3 Course of temperature, asexual-parasite count and sexual-parasitemia in the patient, a 29-year-old Japanese male with ovale malaria (Case 3). The patient was given an oral compound of trimethoprim-sulfamethoxazole (ST) at a dosage of 10 mg TMP/50 mg SMZ/kg Bw in 4 divided doses daily for 4 days, followed by 15 mg primaquine daily for 14 days.

review of the smears the parasites were identified as *P. ovale* as previously reported (Matsumoto *et al.*, 1986). There were 200 parasites/ μ l with 95% trophozoites and 5% gametocytes. A hemogram on 2 June recorded Hb of 15.4 g/dl; Ht 46.1%; Plts 33.1×10^3 ; RBC 458×10^4 ; WBC 4,000 with 47% neutrophils, 24% lymphocytes, 27% monocytes and 2% eosinophils. On 4 June the highest parasite count (53,648/ μ l with 99.2% trophozoites, 0.4% schizonts and 0.4% gametocytes) and the highest temperature (40.7°C) was recorded. A hemogram on 6 June recorded Hb of 13.4 g/dl; Ht 40.1%; Plts 97.0×10^3 ; RBC 445×10^4 ; WBC 6,400 with 84% neutrophils, 9% lymphocytes and 6% monocytes. Intermittent tertian paroxysms peaking at midnight became marked. Liver function tests and other routine biochemistry which were done on 3 and 6 June were almost normal except for total bilirubin (1.7 mg/dl on 3 June and 2.3 mg/dl on 6 June), cholesterol (102 mg/dl on 6 June) and total protein (6.2 g/dl on 3 June and 5.8 g/dl on 6 June). A physical examination on 6 June showed moderate enlargement of the spleen and the liver.

History: The patient had stayed in Kenya from June 1978 to March 1979, July 1980 to February 1981, August 1981 to October 1981 and July 1982 to the end of February 1983. Most of his time was spent in the Turkana district doing anthropological investigations. During his first visit, he irregularly took chloroquine for prophylaxis but he suffered from a malaria-like attack and was cured with sulfamonomethoxine. During his following stays in Kenya, he regularly took a prophylactic drug (chloroquine) against malaria. Until 29 May 1983, no further malarial attacks had been experienced.

Treatment: On 7 June 1983, he was started on 9 oral tablets of TMP-SMZ in 4 divided doses daily (10 mg TMP/50 mg SMZ/kg Bw/a day) for 4 days. Beginning 12 June, 15 mg primaquine was given daily for 14 days.

An examination on 7 June, done just prior to this treatment, revealed a parasite count of 2,993/ μ l of blood with 79.5% trophozoites and 20.5% gametocytes. Asexual-parasite count became 0/ μ l within 36 hours after the first dose was given and disappeared after this time. Sexual-parasite count became 0/ μ l 3.5 days after the beginning of treatment. Since then no parasites were observed on thin films. At midnight on the first day of treatment the temperature was 40.1°C. After that the temperature became normal. Daily hemograms revealed anemia, with the Hb gradually falling to 10.6 g/dl on 11 June. A hemogram on the same day recorded Ht 33.8%, RBC 345×10^4 , Retic 2.1%, Plts 116×10^3 and WBC 4,800. After that the hemogram gradually returned to normal. A hemogram on 27 June recorded Hb of 14.0 g/dl; Ht 41.9%; RBC 465×10^4 ; Plts 187×10^3 ; WBC 4,900 with 54% neutrophils, 26% lymphocytes, 13% monocytes, 5% eosinophils and 1% basophils. Liver function tests and other routine biochemistry were all normal. No parasites were observed on thin films. No symptomatic adverse reactions to TMP-SMZ were observed. A hemogram on 29 May 1984, just one year after the onset of the illness, recorded Hb of 17.2 g/dl; Ht 51.5%; RBC 521×10^4 ; Plts 175×10^3 ; WBC 6,700 with 63% neutrophils, 24% lymphocytes, 8% monocytes, 4% eosinophils and 1% basophils. To date, no relapse has been experienced.

Case 4 (*Falciparum malaria*) (Figure 4)

Present illness: A 48-year-old Tanzanian male developed fever on 5 August 1984 and visited the Department of Medical Zoology, Kyoto Prefectural University of Medicine on 9 August for consultation. He was diagnosed as falciparum malaria and immediately hospitalized in Kyoto Municipal Hospital. Parasite count was 4,371/ μ l of blood with 99.3% trophozoites and

Figure 4 Course of temperature, asexual-parasite count and sexual-parasitemia in the patient, a 48-year-old Tanzanian male with falciparum malaria (Case 4). The patient was given an oral compound of trimethoprim-sulfamethoxazole (ST) at a dosage of 16 mg TMP/80 mg SMZ/kg Bw in 3 divided doses daily for 3 days.

0.7% gametocytes. The highest parasite count (21,476/ μ L) was recorded on 11 August and the highest temperature (39.7 $^{\circ}$ C) was recorded on 10 August. A hemogram on 10 August recorded Hb of 14.2 g/dL; Ht 42.9%; RBC 501×10^4 ; Plts 243×10^3 ; WBC 5,600 with 53% neutrophils, 40% lymphocytes, 3% monocytes and 5% eosinophils. Liver function tests and other routine biochemistry which were done on 10 August were almost normal except for triglyceride (208 mg/dL), LDH (260 U/L) and CPK (125 U/L).

History: The patient was born and raised in Tanzania and did not leave the country until 1959. He stayed in the U.S.A. from 1959 to 1976. After he had returned to Tanzania, he suffered an attack of malaria (date unknown). He arrived in Japan on 30 April 1984. The next day, he developed malarial symptoms (fever and headache). From that time until 5 August, he experienced 7 attacks at two-week intervals. In early June he took a total dose of 2 g chloroquine sulphate (Nivaquine®) over 4 days. The fever disappeared but the headache remained. On 15 July, he took 400 mg amodiaquine (Camoquin®) daily for 3 days. After that he took 400 mg amodiaquine once a week until 5 August.

Treatment: Beginning 11 August 1984, he was started on 14 oral tablets of TMP-SMZ in 3 divided doses daily (16 mg TMP/80 mg SMZ/kg Bw/a day) for 3 days.

An examination on 11 August, done just prior to this treatment, revealed a parasite count of 20,440/ μ L with 99.9% trophozoites and 0.1% gametocytes. Asexual-parasites disappeared within 40 hours after the first dose was given, but sexual-parasites remained for more than 20 days. On the first day of treatment, the temperature was 39.2 $^{\circ}$ C but after that returned to normal. A hemogram on 13 August, 40 hours after the beginning of treatment, recorded Hb of 13.6 g/dL; Ht 40.2%; RBC 472×10^4 ; Plts 172×10^3 ; WBC 4,900 with 42% neutrophils, 43% lymphocytes, 6% monocytes and 9% eosinophils. Blood examination was done on 17, 23, 28

and 30 August; 8, 14 and 26 September; and 2 October. Hb ranged from 14.7 g/dl on 28 August to 15.8 g/dl on 2 October; Ht ranged from 42.5% on 23 August to 45.5% on 14 September and 2 October; RBC ranged from 486×10^4 on 23 August to 536×10^4 on 14 September. Liver function tests and other routine biochemistry were almost normal except for CPK (136 U/l). A slight eosinophilia (8–12%) persisted throughout the examination period. This was considered to be due to concurrent *Necator americanus* infection. No symptomatic adverse reactions to TMP-SMZ were observed. No recrudescence has been experienced until April 1985, when the patient returned to Tanzania.

Serum was analyzed for antibodies against malarial parasites by the IFA test; the serum dilution end-points were 1:1,024 on 10 August and 1:256 on 17, 24 and 30 August against *P. falciparum* and 1:64 on 17 August and 1:16 on 10, 24 and 30 August against *P. vivax*.

DISCUSSION

Trimethoprim-sulfamethoxazole (TMP-SMZ) in a fixed-ratio compound (TMP : SMZ = 1 : 5), sometimes designated co-trimoxazole, is listed as an alternate choice for treatment of infections due to a variety of microorganisms. One normal strength tablet usually contains 80 mg TMP and 400 mg SMZ. This has been marketed under various trade names. The usual recommended dose for adults is 2 tablets twice daily.

Trimethoprim (2, 4-diamino-5-[3, 4, 5-trimethoxybenzyl] pyrimidine), one of the pyrimidine derivatives, is a potent inhibitor of the enzyme dihydrofolate reductase (DHFR) in microorganisms and interferes competitively with the conversion of dihydrofolic (folic) acid to tetrahydrofolic (folinic) acid. Trimethoprim has a particularly high affinity for bacterial DHFR but binds less tightly to the corresponding mammalian enzyme. Sulfamethoxazole (3-[*p*-amino-phenylsulfonamido]-5-methylisoxazole), a semi-long-acting sulfonamid, is a structural analog of *p*-aminobenzoic acid. Sulfamethoxazole competitively inhibits the utilization of *p*-aminobenzoic acid in the synthesis of dihydrofolic acid (folic acid) by microorganisms (Salter, 1982; Wormser and Keusch, 1979). In vitro, these agents are shown to be decidedly more active together than either drug is alone because of sequential blockade of the folate pathway. The efficacy of TMP-SMZ in toxoplasmosis (Grossman *et al.*, 1978), leishmaniasis (Kandil, 1973), *Pneumocystis pneumonia* (Hughes *et al.*, 1975; Harris *et al.*, 1980), and malaria has been demonstrated by various researchers (Salter, 1982).

For treatment of vivax malaria, there are only 2 studies on imported cases in Japan by Yoshioka and Kosaka (1978) and Yamaguchi *et al.* (1986), and on resident populations of endemic areas by Minhas and Siddiq (1971) in Pakistan and by Lal (1982) in Punjab, India. Using a standard daily-dosage of 4 tablets of TMP-SMZ for 5 days on adult patients, Minhas and Siddiq demonstrated that fever resolved within 48 hours and parasitemia disappeared in a mean of 1.8 days. Lal compared the responses of parasitemia and fever in resident children with vivax malaria to standard doses of chloroquine and to different dosage schedules of TMP-SMZ. His study showed that chloroquine produced the most rapid clearance, followed by TMP-SMZ in high daily-dose schedules (8 tablets/day for 2 days or the same dosage followed by 4 tablets/day for 3 days), and then TMP-SMZ in standard dose schedules (4 tablets/day for 3 or 5 days). In Japan, Yoshioka and Kosaka (1978) used 4 tablets/day of TMP-SMZ for 7 days, and Yamaguchi *et al.* (1986) used 4–8 tablets/day for 1–4 days, both with successful elimination of the parasite from the blood. In our cases of imported vivax malaria, Case 1 was given 12 tablets/day (16 mg

TMP/80 mg SMZ/kg Bw/day) for 3 days and Case 2 was given 8 tablets/day (16 mg TMP/80 mg SMZ/kg Bw/day) for 3 days, then both were followed by 15 mg primaquine daily for 14 days. This schedule succeeded in producing radical cures. Asexual-parasites disappeared from the blood of Case 1 in 24 hours and of Case 2 in 48 hours.

Until this study, no studies of the effects of TMP-SMZ on ovale malaria had been published. Nine tablets/day (10 mg TMP/50 mg SMZ/kg Bw/day) for 4 days followed by 15 mg primaquine daily for 14 days succeeded in producing a radical cure. Asexual-parasitemia disappeared within 36 hours and fever resolved within 24 hours.

The efficacy of co-trimoxazole in falciparum malaria has been demonstrated by various researchers (Benjapongs *et al.*, 1970; Wolfensberger, 1970; Fasan, 1971; Yamaguchi *et al.*, 1986). Benjapongs *et al.* (1970) gave TMP-SMZ (4 tablets daily for 2.5–10 days) to previously-untreated acute falciparum malaria and previously-treated chloroquine-resistant malaria. With the 2.5 day schedule, results were unsatisfactory in both groups. With 4 tablets daily, fever resolved in an average of 3 days and asexual-parasites disappeared from blood in 4.3 days. They concluded that, to get the best therapeutic results, treatment should be continued at least 2 days after the disappearance of parasites from blood; that is, the total dosage required to achieve a "complete effect" was 30 to 40 tablets. The clinical response to the same dose was somewhat faster in patients with previously-treated chloroquine-resistant falciparum malaria. Wolfensberger (1970) used 8 tablets daily for 3–4 days in patients with acute falciparum malaria; the TMP-SMZ compared favorably with chloroquine. Fasan (1971) used a single dose of TMP-SMZ in falciparum malaria in semi-immune Nigerian schoolchildren aged 5–12 years. The dose (8 mg TMP/40 mg SMZ/kg Bw) was found to be effective. Fasan also found that half dosages of the same compound were effective. Yamaguchi *et al.* (1986) treated 2 imported cases of falciparum malaria in Japan, one with TMP-SMZ 4 tablets 3 times a day followed by chloroquine diphosphate 600–450 mg/day for 4 days, and the other with TMP-SMZ 3–8 tablets/day for 4 days. They both recovered completely. Falciparum malaria, Case 4 of our study, was presumed to be somewhat resistant to amodiaquine; however, it responded well to TMP-SMZ at a dosage of 16 mg TMP/80 mg SMZ/kg Bw/day for 3 days. Asexual-parasitemia disappeared within 40 hours and fever resolved within 24 hours.

The only study on malarial malaria has been done by Fasan (1971). However, their patients had mixed infections of *P. falciparum* and *P. malariae*. He noticed that there was a reappearance of quartan parasites 3 days after single doses of TMP-SMZ (4 mg TMP/20 mg SMZ/kg Bw). He proposed 2 possible reasons. One is that the individual parasites noted were gametocytes, which in the case of *P. malariae* were difficult to differentiate in a thick film. The other is that TMP-SMZ at this low dosage was less effective against quartan malaria parasites.

In the treatment of malaria, TMP-SMZ has been considered to be a rapidly acting schizonticide. It has been noted that *P. falciparum* crescents were detected as late as one to 2 weeks after treatment with TMP-SMZ, otherwise the response was good. Benjapongs *et al.* (1970), concluded that TMP-SMZ had no effect on gametocytes of *P. falciparum* and therefore primaquine should be prescribed for malaria patients with TMP-SMZ to prevent transmission. In our observation, *P. falciparum* gametocytes were not cleared from the blood of a patient who received TMP-SMZ until 3 weeks following treatment, otherwise the response was good. Gametocytes of *P. vivax* and *P. ovale*, however, might be cleared from the blood of patients by TMP-SMZ, because they disappeared before starting administration of primaquine.

The combination is generally well tolerated even with a large dose of long term administration, as seen in treatment of *Pneumocystis* infection (20 mg TMP/100 mg SMZ/kg Bw/a day for 14 days) (Hughes *et al.*, 1975) or prophylaxis against it in children (4 mg TMP/20 mg SMZ/kg Bw/a day over months) (Harris *et al.*, 1980). The most common adverse reactions are mild gastrointestinal symptoms including nausea, vomiting, and less frequently diarrhea, cramps, glossitis, stomatitis, or jaundice (Salter, 1982; Wormser and Keusch, 1979). Regarding the use of TMP-SMZ for malaria, Benjapongs *et al.* (1970) reported slight nausea and vomiting (in 2 of 5 patients) during the first few days on the 3-tablets-daily schedule and noted one case of mild transient leukopenia. Lal (1982) reported vomiting was noted in 13 of 98 cases, although vomiting was notably common with chloroquine. In our study, no such adverse reaction to TMP-SMZ was observed.

A number of hematologic abnormalities including thrombocytopenia, leukopenia and anemia (macrocytic, megaloblastic, hemolytic or aplastic) have been described in patients receiving TMP-SMZ but they are rare (Salter, 1982; Wormser and Keusch, 1979). Patients with known folic acid or vitamin B₁₂ deficiency are at increased risk from the antifolic effects of the drugs, and patients with questionably adequate folic-acid stores, such as pregnant women, the elderly, patients with malabsorption or malnutrition, or those with chronic hemolysis (such as sickle-cell disease), should be carefully observed. In this study, all patients showed anemia during the treatment but recovered soon after the treatment. This might be mainly due to malarial infection itself.

In conclusion, our study showed that TMP-SMZ may be a safe choice to produce radical cures for malaria caused by any species of malarial parasites, at least vivax, ovale and falciparum malaria at the dosage described above. Trimethoprim-sulfamethoxazole should be examined further in the treatment of chloroquine-resistant malaria and in those countries in which anti-malarial drugs are not easy to obtain.

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トリメトプリム・サルファメトキサゾールによる三日熱、卵型 および熱帯熱マラリア症例の治療成績

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わが国における輸入マラリア症例は年々、増加の傾向にあるが、現在世界で用いられている抗マラリア剤の殆どのものが市販されていない。ところがわが国でも市販されているトリメトプリム (TMP) とサルファメトキサゾール (SMZ) の合剤が三日熱および熱帯熱マラリアに有効なことが知られてきた。われわれも1981年以来経験した4症例に本剤を用いたところ良好な治療効果を得た。まず2例の三日熱マラリアに対して、16 mg TMP/80 mg SMZ/kg/日を分3し3日間投与し、続いてプリマキン 15 mg/日を14日間投与した。1例の卵型マラリアに対しては 10 mg TMP/50 mg SMZ/kg/日を分4し4日間投与し、続いてプリマキン上記量を与えた。さらに1例の熱帯熱マラリアに対しては 16 mg TMP/80 mg SMZ/kg/日を分3して3日間与え、プリマキンは投与しなかった。いずれの例においても発熱など臨床症状は急速に改善し、治療開始36-52時間後の検血で繁殖体は消失していた。生殖母体は熱帯熱マラリアにおいて治療終了後約10日間検出された後消失したが、他のマラリアでは治療期間中に消失した。これらはその後、再発あるいは再燃を示しておらず、本治療で根治したものと思われる。今回は比較的大量を短期間投与したが本剤によると思われる副作用は認めなかった。本剤により卵型マラリアの治療に成功したのは本報告が最初である。以上の成績から本剤は、特に他の薬剤の入手困難な国に於て、また他の薬剤に耐性を生じたマラリアについて有用であると考ええる。

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