Supplemental Folates in the Therapy of Plasmodium falciparum Malaria

LCDR Myron J. Tong, MC, USNR; LCDR Bernhard A. Votteri, MC, USNR; and CAPT Jean-Jacques Gunning, MC, USN

Seventy-five US marines who were treated with pyrimethamine, chloroquine phosphate, and sulfisoxazole for Plasmodium falciparum malaria, were supplemented with either folic acid, folinic acid, or a placebo. A reduced incidence of anemia and leukopenia, a more rapid reticulocytosis, and an increased platelet response were seen in both the folic and folinic acid supplemented groups. The antimalarial effect of pyrimethamine was not inhibited by the addition of folates to the treatment regimen. Folate supplements are recommended when pyrimethamine is used in the therapy of P. falciparum malaria.

ANEMIA, leukopenia, and thrombocytopenia have been noted in patients with malaria, and may become more severe during treatment when chemotherapeutic agents such as pyrimethamine are used.

The present study demonstrates a reduction in incidence of hematologic abnormalities when folate supplements were given to patients treated for Plasmodium falciparum malaria, along with chloroquine phosphate, pyrimethamine, and sulfisoxazole. In addition, no interference with the antimalarial therapy by the folates was observed.

Materials and Methods

Patients.—From March to September 1969, a total of 75 male patients admitted to the Naval Support Activity Hospital, Danang, South Vietnam, with their first infection of P. falciparum malaria were selected for study. All were US marines serving in the First Corps Tactical Zone in South Vietnam. Those with preexisting hematologic abnormalities, such as glucose-6-phosphate dehydrogenase deficiency or a hematocrit value on admission of less than 37%, were excluded.

All patients received an oral regimen of chloroquine phosphate, 1.0 gm initially, and 500 mg every 12 hours for five doses; pyrimethamine 25 mg every eight hours for nine doses; and sulfisoxazole, 500 mg every six hours for six days.

Supplemental Folates.—Patients were randomly divided into three groups with 25 in each group. Daily oral doses of either 5 mg of folic acid, 5 mg of folinic acid, or a placebo were administered in a double-blind fashion for 12 days, commencing on the first day of antimalarial therapy.

Laboratory Tests.—Microhematocrit values were measured in duplicate on venous blood. Reticulocyte counts were determined by counting 1,000 red blood cells in peripheral blood smears stained with methylene blue. White blood cell...
counts (WBC) were measured in a Coulter counter, and platelets were counted with a phase microscope with use of ammonium oxalate as the diluent. Thick and thin malaria smears were prepared with Giemsa's stain. All tests were performed daily for 12 days.

Results

The mean hematocrit readings of patients whose treatment was supplemented with folic acid, folinic acid, or a placebo are shown in Fig 1. Although a decrease in the average hematocrit values was observed in all three groups, the lowest values were found in the placebo-treated patients between the fifth and eighth days. Individual hematocrit values of less than 35%, which represented a decrease of 7%, were demonstrated in 24% (six) of patients in the placebo group (Table). The average reticulocyte counts in all three groups remained at a level of 0.05% until the sixth hospital day, when a gradual increase to 1.6% on the 12th day was observed in both the folic and folinic acid supplemented patients. However, a rise in the reticulocyte counts in the placebo group was not evident until the tenth hospital day.

A decrease in the WBC, reaching an average of 3,600/cu mm on the seventh day, was seen in the placebo-treated patients (Fig 2). Also, individual WBC below 3,000/cu mm were frequently found in this group between the fifth and eighth days (Table). In one patient, the count was as low as 750/cu mm

Hematologic Abnormalities During Antimalarial Therapy*

<table>
<thead>
<tr>
<th>Hematologic Abnormality</th>
<th>WBC &lt; 3,000/cu mm</th>
<th>Platelets &lt; 75,000/cu mm</th>
<th>Hematocrit &lt; 35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>24 (6)</td>
<td>68 (17)</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Folinic acid</td>
<td>0 (0)</td>
<td>20 (5)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Folic acid</td>
<td>4 (1)</td>
<td>28 (7)</td>
<td>32 (3)</td>
</tr>
</tbody>
</table>

*Parenthetical numbers are actual number of patients noted.

2. Mean white blood cell counts of patients whose treatment was supplemented with folic acid, folinic acid, or placebo during malaria chemotherapy.

3. Mean platelet counts of patients whose treatment was supplemented with folic acid, folinic acid, or placebo during malaria chemotherapy.
and remained so for three consecutive days. A majority of the patients in each group had a neutrophilia in the differential count at the time of admission, which was gradually replaced by a predominance of lymphocytes by the 12th day.

An increase in platelet counts occurred in all three groups beginning on the fifth hospital day (Fig 3). However, when compared to the placebo group, patients in both folate supplemented groups had significant rises in their platelet counts from the eighth day which reached average values of 350 to 400,000/cu mm on the 12th day. Platelet counts below 75,000/cu mm were found in approximately equal numbers in each group between the second and fifth days (Table). Bleeding tendencies were not observed in any of the patients.

No differences in clearing of the parasites from the blood were observed in the three groups (Fig 4). Blood smears for the detection of malaria were uniformly negative by the fifth hospital day. Also, the clinical responses to antimalarial therapy were similar in both the folinic and folic acid supplemented and the placebo groups, and all patients were afebrile and asymptomatic after the fifth day.

Comment

The current drug regimens for the treatment of acute *P falciparum* malaria in Vietnam consist of pyrimethamine in combination with quinine or with chloroquine and sulfisoxazole. Anemia, leukopenia, and thrombocytopenia have been noted in patients treated with these regimens, and were attributed to hemolysis and to a temporary bone marrow suppression caused by the malarial parasites and chemotherapeutic agents. Similar hematologic complications were seen in earlier clinical trials with pyrimethamine, and the megaloblastic anemia and pancytopenia which have been described during malaria chemotherapy were attributed to this drug.

Since pyrimethamine acts as a dihydrofolate reductase inhibitor and prevents conversion of folic to folinic acid, the addition of folate supplements to the therapy to prevent hematologic toxicity was suggested. Subsequent studies have shown that folinic acid prevented the appearance of megaloblastosis when pyrimethamine was used in the treatment of toxoplasmosis uveitis. In addition, the antifolate effect of pyrimethamine was fully corrected with folinic acid and partially with folic acid in human bone marrow culture systems.

In this study, patients who were given either folic or folinic acid had a lower incidence of anemia (a hematocrit value of < 35%) and severe leukopenia (WBC < 3,000/cu mm). Although thrombocytopenia (platelet count < 75,000/cu mm) was seen in approximately the same number of patients in all three groups, those whose therapy was supplemented with folates had significant increases in platelet counts from the eighth day on when compared to the placebo group. Also, reticulocyte responses appeared earlier in both of the folate supplemented groups.

No differences in clearing of the parasitemias were observed in the folate-supplemented or placebo-treated patients. This confirmed an earlier report that neither folic nor folinic acid inhibited the antimalarial effects of pyrimethamine, and further suggested that preformed folates are not utilized by the parasites.

The total dose of pyrimethamine used for the treatment of *P falciparum* malaria was 225 mg over a course of three days. Most other studies with pyrimethamine were for longer periods of time, and involved much higher doses. Nevertheless, hematologic abnormalities were consistently seen in our patients. The results from this study have shown that folic acid and folinic acid decreased the incidence of patients with anemia and leukopenia in patients treated with pyrimethamine, chloroquine phosphate,
Pneumocranium From Gunshot Wound of Brain

W. James Gardner, MD, and Edward W. Shannon, MD

A most unusual survival of a gunshot wound of the head was apparently materially favored by an equally unusual treatment aimed at expansion of the area of cerebral defect.

A 36-year-old man was admitted to the hospital on July 7, 1968, exuding torn brain tissue and blood from a shotgun wound of the right side of the forehead. He was unconscious and thrashing wildly with the right arm and leg, while the left extremities were paralyzed. His wife had heard a shot and found him lying on the bedroom floor, his 12-gauge shotgun beside him. She called the police, who delivered him to the hospital within minutes after the shooting. The situation seemed hopeless, but treatment was instituted.

The patient was anesthetized and intubated. A large, extruded mass of lacerated brain tissue was removed, disclosing a 4-cm circular defect in the skull and scalp which was surrounded by extensive powder burns. There was no wound of exit. Aspiration of destroyed brain tissue and blood clot, together with fragments of bone, scalp, shot pellets, and shell wadding, left a cavity 6 to 8 cm in depth which extended laterally from the falx. The patient had falling blood pressure; hemostasis was accomplished with the use of electrocoagulation, hemostatic clips, and oxidized cellulose. Damaged skin edges were excised and tetanus antitoxin was given. Because of the probable incomplete debridement and the poor prognosis, closure was not attempted. The cavity was packed with gauze moistened with 1% neomycin sulfate solution. Transfusions, antibiotics, and diphenylhydantoin sodium were administered. Vital signs progressively improved, and by the fifth day with return of consciousness the endotracheal tube was removed. Drainage of cerebrospinal fluid ceased on the tenth day. Six weeks after injury, sequestration of the exposed outer table of frontal bone was done. Surgical illu—

1. Before application of venous compression, brain surface could not be seen. This exposure made 30 minutes later shows that brain had expanded.

References