THE USE OF PRIMAQUINE IN MALARIA INFECTED PATIENTS WITH RED CELL GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) DEFICIENCY IN MYANMAR

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Abstract. 32 subjects with *Plasmodium falciparum* gametocytes, and 31 cases with *Plasmodium vivax* infection from two military hospitals (Lashio, Mandalay) were treated with quinine 600 mg three times a day for 7 days followed by primaquine 45mg single dose for gametocytes and 45 mg weekly × 8 weeks for vivax malaria. Although screening of red cell glucose-6-phosphate dehydrogenase (G6PD) was done prior to primaquine treatment, G6PD deficient subjects were not excluded from the trial. 20 patients hemizygous for mild G6PD deficiency (Gd^{B-} variant), 2 patients hemizygous for severe deficiency ($Gd^{-Myanmar}$ variant) completed the trial. No case of acute hemolysis was observed in all 22 patients with two genotypes of red cell G6PD deficiency status. Therefore, a single dose of primaquine 45 mg and/or weekly for 8 weeks is adequate for the treatment of patients with *P. falciparum* gametocytes and/or *P. vivax* malaria ignoring these red cell G6PD enzyme deficient variants in Myanmar.

INTRODUCTION

Primaquine (8-amino quinoline) is known to be a very potent gametocidal drug and is active in tissue phase during incubation period and in the latent tissue phase of *P. vivax* and *P. ovale.* It is the only drug capable of eliminating persistent liver forms.

Acute intravascular hemolysis is the most serious toxic hazard due to primaquine, especially in people with erythrocytic glucose-6-phosphate dehydrogenase (G6PD) deficiency. The severity of hemolysis is directly related to the degree of deficiency and to the quantity of primaquine administered. The degree of G6PD deficiency varies greatly, ranging from mild in Africans (African variant A^-) to very high in people of Eastern Mediterranean and west Asian descent (Mediteranean variant B^-) (Clyde, 1981) and in population groups scattered throughout Asia (Asian variants).

Dosages of primaquine given in the treatment of malaria, according to age of the adult patients in different countries were 15mg daily × 5 does in India and Sri Lanka, 22.5mg daily × 14 days in Thailand, 30 mg every third day × 5 doses in Maldives, 45 mg weekly × 8 weeks in Africa and 30mg weekly × 15 doses in Eastern Mediterranean countries, including G6PD deficient patients. A 30 mg single dose, 45 mg single or 15mg daily for 5 days was used in these countries to eliminate gametocytes (Clyde, 1981).

It has been reported in Myanmar that the prevalence of G6PD deficiency in males is 4-14% in various ethnic groups (Aung-Than-Batu and Hla-Pe, 1969) and 15-17% in populations living in malarious areas (Myint-Oo *et al,* 1989). In Myanmar the most com-mon G6PD enzyme variants are Gd^{B-} (mild deficiency; enzyme activity 40-60% of normal) and $GD^{-Myanmar}$ (severe deficiency; enzyme activity less than 5% of normal) (Myint-Oo *et al,* 1991).

Because of the increasing incidence of *P. vivax* infection in Myanmar (Myint-Oo *et al,* 1992) and the occurrence of chloroquine resistant *P. vivax* (Myat-Phone-Kyaw *et al,* 1993), patients with vivax malaria need special attention for radical cure and reduction of transmission. Therefore this study was carried out to see whether primaquine 45 mg weekly dose is less harmful than the previous use of 15mg daily (7.5mg BD) for 14 days in patients with vivax malaria and severe G6PD deficiency. Primaquine 45mg single dose should also used in combination with schizonticidal drugs for the reduction of

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transmission of falciparum malaria.

Although the Myanmar National Drug formulary had recommended a 45 mg single dose for gametocytocidal effect and 45 mg weekly × 8 weeks dose for radical cure of vivax malaria, most medical personnel are reluctant to use primaquine, because of the high incidence of G6PD deficiency.

MATERIALS AND METHODS

118 patients were selected from two hospitals situated in Lashio, No.10 Medical Battalion and Mandalay, No.1 Medical Battalion.

Of 118 malaria parasite positive cases, 20 sujects with *P. falciparum* gametocytes and 10 subjects with *P. vivax* infection were studied under hospitalized conditions.

A field based study was also conducted on 108 subjects selected from Kone Nyaung and Patheingyi areas.

Of 108 malaria parasite positive cases, 12 subjects with *P. falciparum* gametocytes and 21 subjects with *P. vivax* infection were selected for the study.

Examination of blood films and parasite counts were done according to WHO standard methods. The blood smears were taken consecutively for 5 days, then on day 7 and day 14. Hematologic parameters were measured on day 1 to day 5, day 7 and day 14

Methemoglobin reduction test (WHO, 1967) was used to screen G6PD dificiency on admission before treatment. Electrophoretic characterization of G6PD variants was done by starch gel electrophoresis (WHO, 1967) and agarose gel electrophoresis (Myint-Oo *et al,* 1989) for the detection of phenotypic and genotypic alleles of G6PD variants.

RESULTS

Slide positive rates of *P. falciparum* were 18.2% in Lashio, 24% in Mandalay, 30.7% in Kone Nyaung and 12.7% in Patheingyi, respectively. *P. vivax* incidence rates were 8.2% in Lashio, 8.7% in Mandalay, 40% in Kone Nyaung and 13.3% in Patheingyi respectively. There was no significant increase in methemoglobin concentration in both groups (Fig 1). Signs of cyanosis, passage of dark urine and

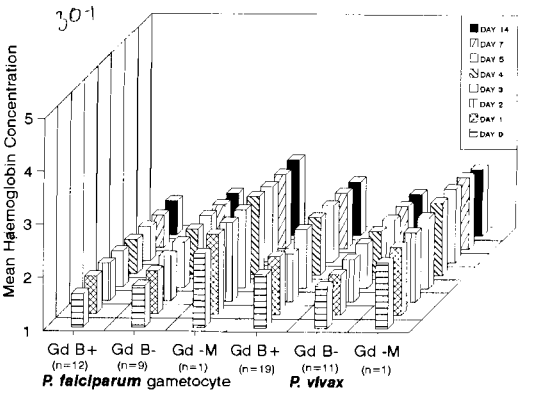

Fig 1–Methemoglobin concentrations before and after primaquine.
Methemoglobin measurements were done before and 6 hours after the adminstration of primaquine 45mg orally.
Gd^{B+} = Normal G6PD enzyme
Gd^{B-} = G6PD mild deficiency (10 to 60% of normal enzyme activity).
$GD^{-Myanmar}$ = G6PD severe deficiency (< 5% of normal enzyme activity).

other symptoms such as epigastric distress, abdominal pain, cramps and vague chest pain were not recorded.

The gametocyte clearance rates and vivax clearance rates were above 50% within 24 hours. There was no relapse on day 14 (Fig 2).

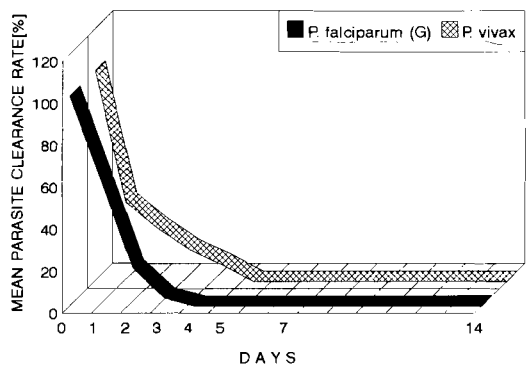

Fig 2–Mean parasite clearance rates (PCR) after primaquine.
PCRs were monitored daily up to 14 days.
P. falciparum gametocyte positive cases = 32;
P. vivax positive cases = 31.

DISCUSSION

Primaquine, along with other oxidant drugs, is able to convert hemoglobin to methemoglobin, producing cyanosis when methemoglobin concentration exceeds 15-20 g/dl of blood (around 10% of the normal level of hemoglobin), the methemoglobin levels in the majority of cases being less than 8.5% of total hemoglobin. It has been reported that methemoglobinemia is generally less pronounced in individuals with erythrocytic G6PD deficiency than in those with normal enzyme levels. This is because the oldest erythrocytes which form most methemoglobin, are also the most susceptible to hemolysis (Clyde, 1981).

In Myanmar, Aung-Than-Batu *et al* (1970) reported 34-48% hemolysis of labeled G6PD deficient erythrocytes that had been injected into normal Myanmar adult males who were given a course of primaquine 15 mg daily. The degree of hemolysis in these individuals was equal to that induced by 30 mg daily in the G6PD deficient African Americans reported by Alving *et al* (1960). Serious hemolysis can occur in patients with G6PD deficiency, when course of 15 mg primaquine daily for 14 days course is administered.

In this study not a single case of hemolysis was recorded in 20 patients with Gd^{B-} variant and in 2 patients with $Gd^{-Myanmar}$ variant by giving 45mg stat dose and weekly doses. There was also no marked change in methemoglobin concentration in 32 G6PD deficient subjects ($p > 0.05$).

It has been reported that the concentration of primaquine in the plasma usually reaches a peak 1-2 hours after oral administration and that G6PD deficiency should not markedly affect the metabolism of the drug (Fletcher *et al,* 1981). Primaquine was completely, or almost completely, removed from the plasma in 24 hours. Thus the destruction of erythrocytes ceases within 4 days of withdrawal of primaquine and maximum causal prophylaxis against vivax malaria occurs within 12 hours after ingestion of a single dose of primaquine (Carson *et al,* 1981).

The absence of manifestations of drug-induced hemolysis in malaria infected patients with G6PD deficiency could be attributed to the following reasons:

(1) Toxicity of primaquine might be dose-related. At the recommended dosage of 45 mg, no symptoms of toxicity were evident.

(2) The method of administration of primaquine : in our study, we observed that a single dose of 45 mg weekly for 8 weeks was better tolerated than a daily dosage of 15 mg for 14 days.

(3) It might also be related to the particular red cell G6PD enzyme variants. So far, no primaquine induced hemolysis has been observed in 22 subjects with either Gd^{B-} variant or $GD^{-Myanmar}$ variant in our study.

In conclusion, we wish to confirm that it is safe to use 45 mg primaquine (weekly for 8 weeks) in patients with *P. vivax* infection and a 45 mg single dose in patients infected with *P. falciparum* gametocytes in Myanmar without measuring the level of G6PD deficiency.

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