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Glucose-6-Phosphate Dehydrogenase Status and Risk of Hemolysis in Plasmodium falciparum-Infected African Children Receiving Single-Dose Primaquine

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Glucose-6-phosphate dehydrogenase (G6PD) enzyme function and genotype were determined in Ugandan children with uncomplicated falciparum malaria enrolled in a primaquine trial after exclusion of severe G6PD deficiency by fluorescent spot test. G6PD A− heterozygotes and hemizygotes/homozygotes experienced dose-dependent lower hemoglobin concentrations after treatment. No severe anemia was observed.

Declines in malaria due to Plasmodium falciparum have been documented in a number of settings where malaria is endemic. It is debated whether scaling-up of conventional malaria control will sustain these declines or achieve elimination unless augmented by tools that specifically reduce transmission. Primaquine is the only currently available drug that actively clears Plasmodium falciparum gametocytes. This was a randomized, double-blind placebo controlled trial with four parallel arms. Ugandan African G6PD mutation (G6PD A−) in a cohort of P. falciparum gametocytes and prevents malaria transmission to mosquitoes (1). The wide-scale use of primaquine is hampered by its hemolytic effect in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The mutation deficiency alters G6PD enzyme function (2), exposing red blood cells to oxidative stress and resultant hemolysis in the presence of a stressor, such as primaquine (3, 4). Primaquine-induced hemolysis is dose related (1, 5, 6). While testing for G6PD deficiency is widely recommended prior to the radical treatment of Plasmodium vivax with 14 days of primaquine, P. falciparum transmission may be considerably reduced by a single, low dose of primaquine (1, 7) and may avoid the necessity to screen for G6PD deficiency. We determined G6PD enzyme function and the presence of the most common African G6PD mutation (G6PD A−; 202A/376G) in a cohort of Ugandan children treated with low-dose primaquine for clearing P. falciparum gametocytes. This was a randomized, double-blinded placebo controlled trial with four parallel arms. Ugandan children 1 to 10 years old with uncomplicated P. falciparum malaria, hemoglobin concentration (Hb) of ≥ 8 g/dl, and normal G6PD enzyme function based on a fluorescent spot test (FST; R&D Diagnostics, Agia Paraskevi, Greece) were enrolled and randomized to treatment with artemether lumefantrine (AL) alone or with a single dose of primaquine at 0.1, 0.4, or 0.75 mg/kg of body weight on the last day of AL treatment (7, 8). Genotyping of G6PD 202A and G6PD 376G was performed (9, 10). Hb was measured on days 0, 1, 2, 3, 7, 10, 14, 21, and 28 after enrollment by HemoCue 201+ (Angelholm, Sweden) and expressed as absolute and relative change compared to baseline values. These values were normally distributed, presented using mean values and standard deviations, and analyzed using linear regression models. Because the age distribution of the red blood cell population influences the severity of drug-induced hemolysis (11), we adjusted all

TABLE 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wild type</th>
<th>Heterozygous</th>
<th>P value for difference from wild type</th>
<th>Homozygous/hemizygous</th>
<th>P value for difference from wild type</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants (% study population)</td>
<td>373 (80.9)</td>
<td>61 (13.2)</td>
<td>27 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% female (no. of females/total no. of participants)</td>
<td>46.7 (174/373)</td>
<td>100.0 (61/61)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age in yrs</td>
<td>5.0 (2.6)</td>
<td>4.8 (2.3)</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) baseline Hb concn in g/dl</td>
<td>11.2 (1.5)</td>
<td>11.4 (1.4)</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% 376G genotype (no. of participants with genotype/total no.)</td>
<td>18.6 (69/371)</td>
<td>78.7 (48/61)</td>
<td>0.0 (0/27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>12.9 (48/371)</td>
<td>21.3 (13/61)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td></td>
<td></td>
<td>100.0 (27/27)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>
comparisons for baseline Hb concentration. All trial participants \((n = 468)\) were G6PD normal by FST. DNA was available for 461 individuals of whom 27 (5.9\%) were homozygous/hemizygous, 61 were heterozygous (13.2\%), and 373 (80.9\%) were normal for the G6PD variant A— (wild type [WT]). All individuals with the 202A mutation also had the 376G mutation, and individuals were classified based on the 202A mutation (Table 1). G6PD 202 A— heterozygous individuals experienced a mean reduction in Hb concentration on day 7 after treatment of 1.08 g/dl (standard deviation [SD], 1.14; \( P = 0.048 \)) in the 0.75-mg/kg treatment arm and 0.99 g/dl (SD, 1.48; \( P = 0.054 \)) in the 0.4-mg/kg treatment arm (Table 2). Homozygous/hemizygous individuals in the 0.75-mg/kg and 0.4-mg/kg arms also experienced a reduction in absolute Hb concentration on day 7, although this was statistically significant in the 0.4-mg/kg arm only (\( P = 0.043 \)). When changes in Hb concentration on day 7 were expressed as a proportion of baseline Hb concentration, the same trend was observed with statistically significant decreases in the 0.75-mg/kg arm for heterozygous individuals and in the 0.4-mg/kg arm for homozygous/hemizygous individuals. No statistically significant changes in absolute or relative Hb concentrations were observed for heterozygous or homozygous/hemizygous individuals in the 0.1-mg/kg arm or placebo arm (Table 2). We found no explanation for the numerically large, but statistically nonsignificant, reduction in Hb concentration in homozygous/hemizygous individuals on day 7 after receiving AL without primaquine. A previous study found no hemolysis after AL in homozygous/hemizygous individuals (12), and we conclude our observation may be a spurious finding and related to our small sample size. Thus, some G6PD-deficient individuals were FST positive despite what would be considered a normal Hb concentration (13). However, a study of G6PD-deficient donors in the United States with FST-positive results found that one donor had a normal Hb concentration (14). Additionally, some G6PD-deficient individuals may have a partial deficiency in their G6PD activity, as determined by FST. Therefore, a reduction in the Hb concentration of G6PD-deficient individuals was not observed in our study, and the effect of primaquine on these individuals is not well understood. We observed statistically significant decreases in Hb following single-dose primaquine in these G6PD-deficient individuals. A hemolytic effect of a single dose of 0.75 mg/kg primaquine base has been reported before (6); our study provides further evidence that primaquine is safe in these individuals. The current findings provide a more comprehensive understanding of primaquine safety in G6PD-deficient individuals, in particular female heterozygotes, who experienced significant reductions in hemoglobin following higher doses of primaquine. The observation that some G6PD-deficient individuals were FST positive but had no symptoms of anemia suggests that some individuals may be at risk of developing hemolysis when treated with primaquine. This study was funded primarily by a Wellcome Trust Bloomsbury Clinical Fellowship to C.D. and T.B. (OPP1034789). We thank the parents and guardians and study participants for their...
REFERENCES


