

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency Status Should be Screened in All Vivax Malaria Patients in Thailand Where Severe G6PD Deficiency is Predominant

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Abstract

Since most G6PD deficiency in Thailand is G6PD Viangchan (which is severe G6PD deficiency), vivax malaria patients coming to seek treatment should be screened for G6PD deficiency before primaquine is given. Primaquine is contraindicated in vivax malaria treatment with severe G6PD deficiency since primaquine may cause massive hemolysis and even death.

Keywords: G6PD deficiency; Vivax; Primaquine; Thailand

Vivax malaria can also cause severe manifestations similar to falciparum malaria and therefore must be adequately treated [1,2]. *Plasmodium vivax* may have relapse due to hypnozoite stage in the liver. Hypnozoites may develop to asexual forms in blood circulation and the patients may have symptoms again (e.g. fever) after anti-malaria drugs for asexual stage treatment (e.g. chloroquine or artemisinin-combination therapy). All drugs for asexual stage treatment could not kill hypnozoites. There has been debate as to whether primaquine should be given in *P. vivax* endemic areas. Repeated vivax malaria relapses are debilitating at any age, but if reinfection is very frequent, then the risks of widespread use of primaquine may exceed the benefits. In low-transmission area such as Thailand, the benefits of deploying primaquine are considered to exceed the risks in the past decades [3]. Reinfection from new mosquito bites was high in high transmission area so the patients may have clinical vivax malaria again from new mosquito bites more than relapse from the previous infection. Therefore primaquine may not be useful in high transmission area. In low transmission area, the patients may have risk to have clinical symptoms from relapse more than reinfection from mosquito bites. Therefore, primaquine is useful for killing hypnozoites and preventing relapse.

Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency is the commonest genetically enzyme deficiency in the world [4-6]. Many variants associated with different enzyme activity have been described and a number of polymorphisms that do not affect enzyme activity. World Health Organization (WHO) has classified G6PD variants into 5 classes according to the wide-type G6PD type B class 1: non-spherocytic hemolytic anemia; class 2: severe deficiency; class 3: moderate deficiency; class 4: no deficiency; and class 5: increased enzymatic activity [5]. The variant G6PD type A is the predominant polymorphism in Africa with equivalent activity to G6PD type B [4]. However, the phenotype-genotype association for many variants is not well defined or is variable between individuals. At present there was no study regarding to classes in predicting safety with primaquine. Residual enzyme activity could inversely correlate with sensitivity to primaquine, but no studies conclusively demonstrate this. The study may be not possible to be conducted in the future due to ethics consideration, e.g. risk of hemolytic crisis and death in severe deficiency with primaquine administration.

Screening for G6PD deficiency in vivax malaria patients is not

generally available outside hospitals in Thailand. There is no G6PD screening tests available in small malaria clinics (belonged to Ministry of Public Health, Thailand (MOPH)) in malaria endemic area along Thai international border (e.g. Thai-Myanmar, Thai-Laos, Thai-Cambodia, Thai-Malaysia border) since MOPH has thought that G6PD deficiency is not an important problem in Thailand. Although G6PD rapid tests are under development, many patients are unaware of their G6PD status. WHO recommends that if a patient is known to have severe G6PD deficiency (e.g. WHO G6PD deficiency class 2), primaquine should not be given since primaquine may cause massive hemolysis and even fatal [4]. In mild-to-moderate GP6D deficiency primaquine might be given in dose of 0.75 mg base/kg body weight (bw) once a week for 6-8 weeks [4,7,8]. However, if significant hemolysis occurred during treatment, primaquine should be stopped. However today clinical practice in Thailand was that when vivax malaria patients was diagnosed by microscopy, chloroquine 25 mg base/kg body weight (bw) divided over 3 days combined with primaquine 0.25 mg base/kg bw, taken with food once daily for 14 days were prescribed. However G6PD deficiency is not screened to all vivax malaria patients by the healthcare workers at malaria clinics in Thailand, the malaria workers just inform patients that if the patients have black colored urine, anemia, or weakness they should go to hospitals, not to malaria clinics again. Therefore malaria clinics have no feedback information how many patients having primaquine adverse effects, e.g. hemolysis. Moreover hemolysed patients may not go to the hospitals due to living far away from their homes. Thai National Policy for vivax malaria treatment has assumed for a long time that most of G6PD deficiency in Thailand is G6PD Mahidol variant which is moderate deficient (WHO G6PD deficiency class 3).

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The study in 1972 [9] found that Mahidol was the common G6PD deficiency variant in Thailand by studying only 22 patients with acute hemolysis. However in 2002, G6PD Mahidol variant was identified less than 10% of G6PD population [10]. The difference between studies [9] and [10], might be explained by the different population surveyed and the technique used in mutation analysis. Another possibility was a lot of people abroad and from neighboring countries came to work in Thailand and contributed to change in prevalences of G6PD deficiency status in Thailand. Nuchprayoon et al. study [10] was based on a relatively large population of unselected individual through cord blood samples at the DNA level, showed better represent the general Thai population, whereas Panich et al. [9] used biochemical assays to assess patients with acute hemolysis.

In study of 522 cord blood samples in Thailand [9], it showed that G6PD deficiency prevalence was 11 % in Thai males and 5.8% in females. G6PD Viangchan was the most common mutation identified (54%) followed by G6PD Canton (10%), G6PD Mahidol (8%), G6PD Kaiping (5%), G6PD Union (2.6%), and G6PD Chinese-5 (2.6%). This study showed that Viangchan was the most common G6PD mutation in Thai population contrasting to previous report [7] showing that G6PD Mahidol was most prevalent. G6PD Viangchan, G6PD Mahidol, and G6PD Canton account for over 70% of G6PD deficiency of Thai people. Regarding to WHO G6PD deficiency classification [5], primaquine is contraindicated and should not be given to vivax malaria patients with severe G6PD deficiency eg., G6PD Viangchan, G6PD Canton, G6PD Kaiping, and G6PD Union since those variants are in WHO class 2 (with severe G6PD deficiency) which account around 70% of G6PD deficiency of people in Thailand (Although other report mentioned G6PD Canton was listed as class 3 [11]). Whereas G6PD Mahidol and Chinese-5 are in WHO class 3 (with moderate deficiency) and unknown class respectively. Therefore, primaquine 0.75 mg base/kg bw once a week for 6-8 weeks may be used in males and non-pregnant females with G6PD Mahidol (which is moderate G6PD deficiency) [8].

There were many Laotian, Cambodian, Mon and Myanmar people came to work in Thailand and some of them had malaria infection after entering malaria endemic area, e.g. forests along Thai international border. Most of vivax malaria patients were treated at malaria clinics (belonged MOPH) or at Thai hospitals without G6PD screening. G6PD deficiency of those foreigners were previously studied and showed that G6PD Viangchan (WHO class 2 (with severe G6PD deficiency)) [12] was the most common mutation among Laotians and Cambodians working in Thailand [6] whereas G6PD Mahidol WHO class 3 (with moderate G6PD deficiency) was the most mutation among Mon and Myanmar people [13]. Difference in the prevalence and distribution of G6PD gene variants was also found among Thai and Myanmar population in different malaria endemic area of Thailand [14,15]. In earlier study in Thailand, daily doses of 15 mg of primaquine for 14 days following a full course of chloroquine when prescribed to Thai G6PD deficient adult patients with predominant G6PD Mahidol variant showed relatively safe although hematocrit was significantly dropped on day 7 of treatment [16]. To prevent hemolysis, vivax malaria patient with G6PD Mahidol variant should be given primaquine as weekly doses rather than daily doses.

Fluorescent spot test (semiquantitative test) is the most acceptable method for screening since it is simple, inexpensive (\$1/test), and suitable for use in the field. However it needs UV light source. In the settings where electricity is of shortage, commercial color reduction kit may be used. The latter is cheaper (\$0.5-0.9/test), easier to perform, less time consuming, and does not require sophisticated equipment

(UV lamp). In female with heterozygote G6PD deficiency, fluorescent spot test may be normal. Methemoglobin reduction test (screening test and quantitative test of G6PD deficiency) may be better diagnosis of G6PD deficiency. However, methemoglobin reduction test may not be possible in the field since it needs instrument and skilled persons to test which is impossible in limited infrastructure settings.

Since there were many G6PD deficiencies with different severity in Thai and non-Thai people living in Thailand at present, it is the right time that Thai health authorities, particularly malaria clinics in malaria endemic area, and hospitals in Thailand must screen G6PD deficiency status in all vivax malaria patients coming to seek treatment. In G6PD deficient patients, severity of G6PD deficiency should be found before primaquine is given. Primaquine may be prescribed as weekly doses for 6-8 weeks in moderate G6PD deficiency; however weekly hematocrit should be monitored before next dose of primaquine given. Primaquine is contraindicated to give to vivax malaria patients with severe G6PD deficiency in order to avoid massive hemolysis.

In conclusion, current status of primaquine across Thailand is primaquine should be used for radical cure in vivax malaria patients with screening tests showing normal G6PD. In patients with G6PD deficiency, 6-8 weekly doses of primaquine should be given in moderate G6PD deficiency whereas in patients with severe G6PD deficiency, primaquine should not be given at all. However weekly hematocrit before next weekly doses of primaquine should be monitored, if hematocrit drops too much or patients have anemic symptoms; next dose of primaquine should be withheld. Fluorescent spot test or commercial color reduction kit (semiquantitative screening test) should be used at all malaria clinics or in the field since they are practical and the cost is not expensive in Thailand. If screening test shows G6PD deficiency, blood should be further sent to central laboratory at provincial level (in some provinces) or regional level to distinguish between moderate or severe deficiency before primaquine is safely given. At present there is no both relevant and practical screening method to distinguish between moderate and severe deficiency. Even quantitative screening methods require at least modest laboratory skills, specialized equipment, and refrigeration. Surveillance/follow-up systems to monitor primaquine tolerance should also be conducted, if possible to then relate this to difference variants and phenotypes. Prevalence of G6PD deficiency variants in population should be regularly updated since there were many neighboring people from Cambodia, Laos, Mon and Myanmar who have predominantly severe G6PD deficiency variants (e.g., Viangchan variant) and moderately G6PD deficiency variants (e.g., Mahidol variant) migrating to Thailand. Thai National policy for vivax malaria treatment with chloroquine and daily dose of primaquine for 14 days to all patients living in Thailand without G6PD screening should be revised as soon as possible.

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