Case Reports

Safety of weekly primaquine in G6PD deficient patient with relapsing vivax malaria: A case report


ICMR-National Institute of Malaria Research, New Delhi, India

Key words G6PD deficiency; Plasmodium vivax; primaquine; relapse

Plasmodium vivax relapses contribute to about half of all the malaria cases reported annually in India. It has unique feature of causing relapses due to persistent liver stages of the parasite (hypnozoites), which makes control of vivax malaria challenging. Relapse rates of up to 40% have been reported from different parts of India. In vivax malaria, relapses are known to dominate over the primary attacks and if 65% of vivax malaria cases are treated with antirelapse therapy, elimination would be possible in a decade.

Currently, primaquine is the only registered and marketed antirelapse agent; however, it is known to cause haemolysis in G6PD deficient individuals. For targeted malaria elimination, it is important to administer primaquine in safe and effective doses in all the vivax malaria cases to prevent relapses. We present a case of vivax malaria with G6PD deficiency, in which primaquine was administered weekly in WHO recommended dosage.

Weekly primaquine was found to be safe in G6PD deficient patient, and there were no clinical or laboratory manifestations of haemolysis.

Case Report

A 23-yr-old male patient reported to malaria clinic at the National Institute of Malaria Research, New Delhi, with positive laboratory report for P. vivax malaria. He was referred by a physician for deciding the line of treatment, since he was G6PD deficient. Blood smear was positive for P. vivax malaria with parasite count of 12,960/µl. He was treated with chloroquine (10 mg/kg on Day 0 and 1; and 5 mg/kg on Day 2). He had three episodes of vivax malaria within a period of six months (Fig. 1). His G6PD level was 1.27 U/g of haemoglobin, around 26% of the lower limit of normal range (4.60–13.50 U/g) of G6PD. Primaquine was not prescribed to him during the previous episodes due to G6PD deficiency.

To prevent further relapses, the patient was advised primaquine in the dose of 0.75 mg/kg body weight every week for 8 wk as per WHO guidelines, which considers it as a safe regimen in G6PD deficiency, under supervision of a physician. Before administering primaquine, haemoglobin level was 13.9 g (at baseline) which dropped to 12.9 on Day 7 of administration. It recovered by third week (Fig. 2). There were no adverse events like nausea, pain in abdomen, dark coloured urine or significant fall of haemoglobin after administering primaquine.

Compliance to weekly primaquine was ensured by making phone calls. After completion of primaquine course for 8 wk, no episode of clinical malaria occurred for one year.
G6PD genotyping was carried out\(^8\) using PCR-RFLP followed by sequencing. The results were analysed with BLAST tool (G6PD accession no. NM_001042351.2, http://ensembl.org) which confirmed the absence of three mutations, i.e. G6PD Mediterranean, G6PD Orissa and G6PD Kerala Kalyan, that are common in India\(^8\) (Fig. 3). However, due to lack of sufficient blood sample, further investigation of G6PD mutation by exon-wise PCR and nucleotide sequencing could not be performed.

**DISCUSSION**

*Plasmodium vivax* relapses contribute to a significant burden of malaria in India. The national antimalarial drug policy of India recommends use of primaquine at dose of 0.25 mg/kg daily for 14 days for preventing relapses. However, it is contra-indicated in G6PD deficient individuals due to its haemolytic potential\(^10\). Primaquine can cause haemolysis in G6PD deficient individuals and even in heterozygous females with G6PD levels 40–60% of normal\(^6,11-12\). As suitable point of care test for G6PD is not available, many practitioners are reluctant to prescribe primaquine due to risk of haemolysis in G6PD deficient patients\(^13\). The Indian national treatment guidelines also recommends primaquine without testing for G6PD but with educating the patient regarding the warning signals of haemolysis and after weighing risks vs benefits of treatment\(^14\).

In this report, a case of relapsing vivax malaria with G6PD deficiency is reported. The patient had three episodes of malaria in last six months, i.e. relapses were observed, 4, 5 and 6 months after the primary episode of malaria (Fig. 1). The relapses occurred in the months of January, February and March 2015. These months have been reported as the months of relapse through a transmission model\(^5\).

In India, frequent as well as long latency relapses have been reported\(^2,15\). WHO has advised use of weekly primaquine as antirelapse therapy in patients with G6PD deficiency. This weekly treatment should be given under medical supervision and patient should have access to health facility with facilities for blood transfusion\(^16\). Primaquine in the dose of 0.75 mg weekly is safe and effective in preventing relapse, since the total dose of primaquine administered matters instead of per dose strength\(^17-18\). There are no reports from India regarding haemolysis due to weekly primaquine therapy in G6PD deficiency. A review of risks and benefits of primaquine mentions that the incidence of serious adverse events with primaquine therapy in known G6PD deficient patients was 11.2%, but a majority of these received a daily dose of primaquine in the dose of 0.25 mg/kg.

**Fig. 3:** Ethidium bromide stained 3% agarose gel showing the restriction enzyme digested amplified products in three common G6PD mutations. Lane 1 sample lacks the digestion site and produced —(a) 377 and 198 bp products in exon 6/7 with *Mbol*; (b) 107, 75 and 66 bp products with *HaeIII*; and (c) 74 and 60 bp products with *MnlI* restriction enzymes respectively. However, Lane 2 (Control) produced —(a) 277, 119 and 100 bp products in exon 6/7; (b) 123, 107 and 66 bp products in exon 3/4; and (c) 80 and 60 bp products in exon 9 upon digestion. M1, M2 and M3—Molecular markers of size 100, 50 and 20 bp respectively; U—Undigested product [575 bp in (a), 352 bp in (b), and 275 bp in (c)]; 1—Patient sample DNA; 2—G6PD deficient controls.
of primaquine\textsuperscript{19}. The drug induced haemolysis in G6PD deficient patient can be related to the variant of G6PD, dose and duration of the medicine, disease factors and patient factors like anaemia\textsuperscript{20}. The patient in this case had a mild G6PD deficiency, low parasite count and was not anaemic, and received a weekly dose; hence, there was no significant fall in haemoglobin.

Globally, few studies have reported safety\textsuperscript{21} and efficacy of primaquine weekly dose\textsuperscript{22} in G6PD deficient subjects. From India, this is the first reporting on safety of ~5 h), and even if haemolysis occurs, it is self limiting\textsuperscript{19}. no episode of haemolysis was observed as Hb levels were weekly primaquine (0.75 mg/kg) was well tolerated and G6PD testing. This creates dilemma in prescribing primaquine without point of care G6PD facilities. Help from the staff of Malaria Clinic of NIMR, New Delhi for providing laboratory facilities. The authors thank the National Institute of Malaria Research (NIMR), New Delhi for providing laboratory facilities. Help from the staff of Malaria Clinic of NIMR is also acknowledged. Thanks are also due to the National Institute of Immunohematology, Mumbai, India for providing training on G6PD genotyping.

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**Conflict of interest**

The authors declare that there is no conflict of interests.

**Ethical statement:** Verbal consent was obtained from patient for weekly primaquine therapy and publication.

**REFERENCES**


