The 8-Aminoquinoline Ineligibles – Pharmacogenetic Barriers to Vivax Malaria Prevention and Treatment

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Abstract
The human malaria caused by *Plasmodium vivax* occurs around the globe, especially in South and Southeast Asia where >80% of all cases occur. After over a century of being considered an intrinsically benign and relatively harmless parasite, recent evidence reveals it as a dangerous and often life-threatening infection. It also happens to be the most difficult form of malaria to properly prevent or treat due to its latency in the form of dormant and undetectable liver parasites called hypnozoites. Those parasites are not impacted by the usual blood schizontocidal therapies applied to arrest the acute febrile attack of malaria – a hypnozoitocide must be applied to prevent multiple recurrent clinical attacks called relapses over the weeks, months, and several years following a single infectious bite by an anopheline mosquito. The only available hypnozoitocidal drugs, primaquine and tafenoquine, are both 8-aminoquinolines and share the class liability of potentially life-threatening hemolytic toxicity in patients having the common inherited disorder called glucose-6-phosphate dehydrogenase (G6PD) deficiency. Patients needing primaquine or tafenoquine therapy must be screened for G6PD deficiency before receiving either drug, and patients who may be pregnant, lactating, or less than 6 mo or 16 yr of age (for primaquine or tafenoquine, respectively) cannot receive these 8-aminoquinolines. Patients lacking access to G6PD screening services may also be ineligible. Finally, recent studies in Indonesia have shown that patients having impaired cytochrome P-450 2D6 isozyme (CYP2D6) very often failed directly supervised high-dose primaquine therapy against relapse of *P. vivax* malaria. Most of them had the phenotypically impaired *10 allele for CYP2D6 which occurs at relatively high frequencies in the limited scope of Asian populations thus far surveyed. As much as 15% of Asian patients may not benefit from standard primaquine therapy against relapsing vivax malaria. Taken together, the problems of primaquine hemolytic toxicity in G6PD-deficient patients and of primaquine failure in CYP2D6-impaired patients disqualify many millions of Asians at risk of infection by *P. vivax* and potentially needing 8-aminoquinoline therapy.