Radical Cure: The Case for Anti-Relapse Therapy Against All Malarias

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(See the article by Douglas et al, on pages 612–620.)

Douglas et al [1] describe patency with *Plasmodium vivax* in the 63 days after treatment of malaria caused by *Plasmodium falciparum* in >10,000 subjects in Thailand over a 14-year period who received 25 different therapies. Therapy for acute malaria aims at the asexual stages of the organism infecting blood. Among the many blood schizontocidal drugs that achieve this therapeutic effect, none eliminate dormant stages in the liver, which are known as hypnozoites. Regardless of the species being treated, if hypnozoites are present, relapse may occur in the absence of treatment with primaquine, which is the only registered hypnozoitocide. The patients evaluated by Douglas et al [1] did not receive hypnozoitocidal therapy for the simple reason that it is not indicated for falciparum malaria. Parasitemia with *P. vivax* occurred in 20%–51% of these patients, with that rate correlated to the rapidity of excretion of drugs administered against *P. falciparum*.

Malaria manifests as many infections of distinct biological character, with susceptibility to distinct classes of drugs, and distinct clinical or epidemiological consequences [2]. Anopheline mosquitoes transmit all of the 5 species of the genus *Plasmodium* known to naturally infect humans. Each passes through a series of liver and blood stages of asexual development that massively expand the numbers of individual parasites. In a biological sense, that expansion aims solely at positioning male and female sexual forms (called gametocytes) where they can access the gut of feeding anopheline mosquitoes—the only site where these parasites execute the sexual recombination essential to their propagation. Humans simply represent a means for the plasmodia to traffic among their mosquito definitive hosts.

Two species of plasmodia infecting humans hedge the probability that biting anophelines will be present to capitalize the relatively risky venture into blood. Among the infectious sporozoites of *P. vivax* and *Plasmodium ovale* introduced by biting anophelines, an unknown and variable fraction arrest development after invading human hepatocytes [3]. These clinically silent hypnozoites later commence development and emerge into the bloodstream to cause another round of malaria, which is termed a relapse.

The probability, interval, and frequency of relapse in the absence of primaquine treatment vary geographically in a manner suggesting linkage to a high probability of a relative abundance of anophelines [4]. Only ~30% of individuals with infection due to *P. vivax* from the temperate Korean peninsula, for example, experience relapse after 8 months and only once; whereas almost all individuals with infections due to *P. vivax* from the perpetually warm and wet climate of New Guinea experience relapse within 4 weeks and experience relapse >5 times. These climate-specific relapse behaviors persist among strains transferred to another hemisphere, and they thus appear to be genetically programmed [3, 4]. In Thailand, ~60% of patients treated for acute vivax malaria with rapidly excreted blood schizontocides experienced relapse within 28 days after patency [5]. When slowly excreted blood schizontocides (eg, chloroquine or mefloquine) were applied, no relapses appeared by day 28, because drug lingering in blood killed the asexual blood stages emanating from activated hypnozoites. When drug levels slip below minimally effective concentrations, relapses may occur [6].
Figure 1. The graph illustrates cumulative incidence (left axis) of relapse among several hundred patients infected with *Plasmodium vivax* from Southeast Asia and the Western Pacific regions and treated with either rapidly excreted quinine (solid points) or slowly excreted chloroquine (hollow points). Blood levels of chloroquine and its major metabolite desethylchloroquine (right axis) slowly decrease to below the minimally effective concentration (MEC) at approximately day 35, coinciding with commencement of relapse. Reproduced with permission from Baird [7]. Antimicrob Agents Chemother 2004; 48:4075–83. Copyright American Society for Microbiology.
enable safer and more-effective treatment against hypnozoites. Such a tool would also raise the possibility of treating all patients with malaria, regardless of the species diagnosed, with anti-relapse therapy.

The division of prescribed therapies across species of plasmodia may derive from practice in zones where malaria is not endemic. Most patients with malaria who are seen in that setting (e.g., travelers) likely had a single encounter with an infected anopheline mosquito and will usually harbor a single species. In zones of endemicity, however, patients have cumulative exposures. If Thailand, where the disease is endemic, is typical, then more than half of patients are co-infected with at least 2 species. The people in any given community in which the disease is endemic who are demonstrated to be at risk with 1 species (by diagnosis) are also at risk for infection by the other species (whether infection due to that species is diagnosed or not) [14–16]. It stands to reason that patients with falciparum malaria in Thailand had a high risk of co-infection with hypnozoites of P. vivax, because these sympatric parasites share the same human and mosquito hosts. The data reported by Douglas et al [1] and the data reported by others and summarized by them should remove doubt on this important point. Providing therapy that is effective against P. falciparum but not against P. vivax is reasonable only when treatment is hamstrung by the toxicity of primaquine.

Confidence in the safety of primaquine therapy in most patients should prompt consideration of anti-relapse therapy after a diagnosis of P. falciparum malaria in areas in which this species occurs with P. vivax. This approach could provide a complete solution to the problem of relapse in zones of malaria endemicity. Fielding an RDT for G6PD deficiency that provides certainty of primaquine safety could revolutionize chemotherapeutic strategy and efficacy in zones of malaria endemicity. There may be no more important task than this across the broad array of work required to control and eliminate malaria.

Acknowledgments

Financial support. The Wellcome Trust. Potential conflicts of interest. Author certifies no potential conflicts of interest.

References

1. Douglas, et al.
2. Baird JK. Eliminating malaria—all of them. Lancet 2010; 376:1883–8.
3. Shute PG, Lupascu G, Branzei P, et al. A strain of Plasmodium vivax characterized by prolonged incubation: the effect of numbers of sporozoites on the length of the prepatent period. Trans R Soc Trop Med Hyg 1976; 70:474–81.
4. Contactos PG, Collins WE, Jeffery GM, Krotoski WA, Howard WA. Studies on the characterization of Plasmodium vivax strains from South America. Am J Trop Med Hyg 1972; 21:707–12.
5. Pukrittayakamee S, Chantra A, Simpson JA, et al. Therapeutic responses to different antimalarial drugs in vivax malaria. Antimicrob Agents Chemother 2000; 44:1680–5.
6. Baird JK, Leksana R, Masbar S, et al. Diagnosis of resistance to chloroquine by Plasmodium vivax: timing of recurrence and whole blood chloroquine levels. Am J Trop Med Hyg 1997; 56:621–6.
7. Baird JK. Chloroquine resistance in Plasmodium vivax. Antimicrob Agents Chemother 2004; 48:4075–83.
8. Coatney GR, Collins WE, Warren M, Contactos PG. The primate malarials. Washington, DC: US Government Printing Office, 1971:37.
9. Eyles DE, Young MD. Studies on imported malaria; the parasitological pattern of relapsing Plasmodium vivax in military patients. J Natl Malar Soc 1948; 7:23–37.
10. Hill E, Amatuzio DS. Southeast Pacific vivax malaria; clinical features and observations concerning duration of clinical activity. Am J Trop Med Hyg 1949; 29:203–14.
11. Alving AS, Johnson CF, Tarlov AR, et al. Mitigation of the hemolytic effect of primaquine and enhancement of its action against exoerythrocytic forms of the Chesson strain of Plasmodium vivax by intermittent regimens of drug administration. Bull World Health Organ 1960; 22:621–31.
12. Schmidt LH, Fradkin R, Vaugh D, Rasco J. Radical cure of infections with Plasmodium cynomolgi: a function of total 8-aminoquinoline dose. Am J Trop Med Hyg 1977; 26:1116–28.
13. Baird JK, Rieckmann K. Can primaquine therapy for vivax malaria be improved? Trends Parasitol 2003; 19:115–20.
14. Mayxay M, Pukrittayakamee S, Newton PN, White NJ. Mixed species malaria infections in humans. Trends Parasitol 2004; 20:233–40.
15. Brown AE, Cain KC, Pipithkul J, Webster HK. Demonstration by the polymerase chain reaction of mixed Plasmodium falciparum and P. vivax infections undetected by conventional microscopy. Trans R Soc Trop Med Hyg 1992; 86:609–12.
16. Siripoon N, Snounou G, Yamogkul P, Na-Bangchang K, Thaithong S. Cryptic Plasmodium falciparum parasites in clinical P. vivax blood samples from Thailand. Trans R Soc Trop Med Hyg 2002; 96:70–1.