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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]. Anophele mosquito 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 anophele 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].
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 (eg, 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 G6PDd 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.

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References