EDITORIAL A RARE GLIMPSE AT THE EFFICACY OF PRIMAQUINE

J. Kevin Baird
ALERTAsia Foundation, jkevinbaird@yahoo.com

Follow this and additional works at: http://digitalcommons.unl.edu/publichealthresources

http://digitalcommons.unl.edu/publichealthresources/358

This Article is brought to you for free and open access by the Public Health Resources at DigitalCommons@University of Nebraska - Lincoln. It has been accepted for inclusion in Public Health Resources by an authorized administrator of DigitalCommons@University of Nebraska - Lincoln.
Primaquine, the only tool in our drug toolbox for preventing relapse of *Plasmodium vivax* or *P. ovale* malaria, may be the most enigmatic of the most commonly prescribed drugs today. Despite more than 50 years of continuous use by millions of people each year, we do not understand how it works. Its complex metabolism generates a dozen known metabolites, and none of these has been definitively linked either to its potent activity against hypnozoites or to its hemolytic toxicity to people having an inborn deficiency of glucose-6-phosphate dehydrogenase.

The drug is a poster child for neglect of basic and applied research bearing directly upon one of the most prevalent parasitic infections of the tropics. How many common infections in the developed world have only a single therapy available, and one that has been around for more than 50 years? How many of those therapies have unknown mechanisms of activity? Even worse, is there any therapy prescribed against developed world infections that we do not know if the drug is actually working?

The current efficacy of primaquine against relapses by *P. vivax* malaria, proven more than 50 years ago in clinical trials, is almost completely unknown. The evaluation of the therapeutic efficacy of primaquine against relapse has long been in the “too hard to do box.” And it is hard. *Plasmodium vivax* malaria presents daunting confounders, as well as logistical and ethical obstacles against evaluating drugs preventing relapse. Molecular markers to distinguish relapse from either reinfection or recrudescence provide only ambiguities. Chloroquine as a companion blood schizonticide may not be relied upon to clear the bloodstream of parasites where resistance to it occurs, and its lingering blood levels may effectively clear chloroquine-sensitive parasites emerging from primaquine-resistant relapses. Finally, a series of early clinical trials suggested primaquine might require chloroquine or quinine to achieve its potent killing of formed hypnozoites.

There is no validated procedure for demonstrating resistance to primaquine, but it would look something like this: primaquine administered with quinine under direct supervision of subjects who must be followed for at least 60 days in areas where reinfection is highly unlikely. Moreover, the natural relapse rate for the area would have to be known beforehand, or, ideally, evaluated in randomized fashion in people receiving only quinine therapy. This approach, in my hands, consistently failed to clear ethical committees in Indonesia and the work was never done. Another approach, experimental challenge of human subjects, faces perhaps less daunting ethical challenges but imposes relatively huge costs.

Epidemiology offers another approach to examining the efficacy of primaquine. Twelve years ago in the *American Journal of Tropical Medicine and Hygiene*, Jelinek and others published a study of primaquine therapy among Euro-

