Malaria Chemoprophylaxis for the Long-Term Traveler in Southeast Asia

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Long-term travelers present particular problems where compliance with drug regimens, side effects, and drug resistance are concerned, in that these problems are inevitably magnified by increasing time scales. Many long-term travelers abandon all attempts at malaria prevention after experiencing a few real, or imagined, drug side effects or the inconvenience of many drug regimens is discovered. Therefore, it is important to recommend actions that can actually be executed under realistic circumstances and that reflect the actual risk of malaria to the traveler.

The epidemiology of malaria in Southeast Asia is markedly different from the more familiar holoendemic areas of tropical Africa or New Guinea. In Southeast Asia, malaria tends to be an extremely focal disease. Because of the anopheline vector, malaria tends to be closely associated with jungles and mountains. Undisturbed forest is not a requirement of the mosquito vector, which needs only small shaded pools of water. Therefore, malaria maps of some countries in Southeast Asia may resemble donuts. The highly endemic zones are confined to uncontrolled border areas, with the central rice growing areas remaining relatively malaria free. This situation is not universal, but it does provide a rough guide. A good example is that of aid workers, who have almost no malaria risk while working in a central urban office, but who are at risk when traveling to field sites, particularly when a night must be spent in a forested area. Similarly, soldiers are often on unit rotation systems, such that some companies on border guard duty will be at high risk of infection, while other companies only 5–10 km away will show almost no new infections. This effect is often blurred when partially suppressed infections recrudesce or *P. vivax* infections reoccur to produce clinical malaria episodes removed in time from the occurrence of the actual infection.

The type of traveler has a lot to do with his or her expected malaria risk. Access to reliable health care varies considerably throughout the region, and this is a key question when deciding on what degree of malaria risk can be tolerated in a long-term traveler. Travelers and businessmen, who never leave the capital city (Bangkok, Phnom Penh), essentially have a zero risk of contracting malaria. Mosquito repellent and other avoidance measures alone are satisfactory for very limited exposures. Aid workers, however, are very heterogenous and can vary from the logistics chief, who never leaves the capital, to the field worker, who lives in the jungle. Most aid workers fall somewhere in between, with episodic, but not constant, exposure to malaria. How to obtain a realistic estimate of malaria risk, especially since physicians must give advice prospectively, usually to a traveler who knows his or her general job description but little else about their destination, is difficult. Advice is at best, a guess, and often reflects willingness on the part of the traveler to take medication more than on any other factor. Military units have an advantage in that one can refer to earlier experiences of the same unit for guidance. In the United Nations Transitional Authority Cambodia (UNTAC) force in Cambodia for instance, the bulk of troops are in the cities of Battambang and Phnom Penh, and those who stay there have very little malaria risk. This is different from those personnel sent to small border-control check points, particularly along the Thai and Vietnamese borders.

The perfect malaria chemoprophylactic drug does not exist, and most regimens represent a compromise between efficacy and compliance. Currently there are two tested regimens that can be recommended in Southeast Asia: weekly mefloquine and daily doxycycline. The best operational efficacy using either drug for highly exposed military units along the Thai-Cambodian border, with enforced compliance, is about 1% attack per week during the peak transmission season,[1,2] which gives an estimated efficacy of about 80%. The situation with mefloquine is rapidly

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deteriorating because of the spread of intense mefloquine resistance. How long either regimen can be maintained is an important but unanswered question. Mefloquine prophylaxis lasting up to 6 months has shown few untoward effects. Longer-term administration in US Peace Corps members indicates weekly mefloquine is well-tolerated.[3,4] The rare central nervous system symptoms associated with mefloquine appear early and do not appear to increase with time or be directly related to blood drug concentration.[5] With doxycycline the situation is both easier and harder. Many adolescents have taken daily doxycycline for many years for acne without unusual side effects. The real problem in extrapolating these observations to malaria prophylaxis is that the dosage is usually 50 mg daily for acne as opposed to 100 mg for malaria. Compliance with daily doxycycline is also extremely difficult to maintain, except in compulsive individuals. Reports from UNTAC demonstrate that groups apparently tolerate doxycycline for up to 1 year, but this may reflect either lack of side effects or merely failure of drug administration.

Episodic exposure of individuals to malaria, and thus antimalarials, may have contributed to the propensity of Southeast Asian strains of malaria to develop drug resistance. Cross-border gem mining in Cambodia, which necessitates frequent short trips into the mining areas of persons either partially covered, or inadequately treated, with mefloquine, has certainly degraded mefloquine's efficacy. The episodic use of doxycycline in persons with infrequent defined periods of malaria risk, is one approach to handling the diplomatic corps member or aid worker who usually lives in a low-risk area, but whose job occasionally exposes him to malaria. This approach may be particularly appropriate for persons with access to good health care facilities, except during their field trips. Industries, particularly businesses involved with mineral and timber extraction, which necessitates employees living and working in intensely malarious areas for long periods of time, present a complex problem with no clear solution. Missionaries, particularly those with families, also have no obvious solution to combat constant malaria exposure. Apparently, mefloquine can be taken for a long period of time and, in the past, did provide reasonable protection. Currently, however, the situation with mefloquine resistance is such that one cannot recommend relying on it in Southeast Asia. Asking nonpregnant adults to take doxycycline for months to years is safe, but probably unrealistic unless some kind of enforced compliance mechanism exists such as the case in the Military. Children under ten generally pose a problem due to the paucity of pediatric research addressing questions specific to childhood. Proguanil combined with sulfamethoxazole has been shown to work on the Thai-Burmese border, but this was prior to the introduction of multiple drug-resistant falciparum malaria.

One particularly worrisome possibility in the UNTAC forces is that multiple drug-resistant malaria could be carried via troop rotations from Cambodia into other malarious areas where hyperresistant strains do not yet exist. Other parts of Southeast Asia, such as Indonesia and Malaysia or tropical Africa, are at least at theoretic risk. The example of late mefloquine failures in the Dutch Marines does not inspire confidence. A few percent of marines developed recrudescent falciparum malaria in Holland weeks after discontinuing mefloquine prophylaxis. Although nonimmunes in a developed country are unlikely to carry infective gametocytes near many anophelines, this may not be true in other areas where partial immunity, declining drug levels, and lack of clinical diagnostic facilities may result in the movement of resistant strains across whole continents in a single person. What can actually be done to limit this frightening possibility? Quarantine in a nonmalarious area during the period of discontinuing a prophylactic drug would certainly work, but this measure is rejected by most as impractical and expensive. Eradication courses of primaquine generally work against relapsing malaria, but not against the more worrisome falciparum malaria. Short courses of 3 or 6 days of postexposure halofantrine was somewhat successful in New Guinea copper miners, who were returning from holidays in highly endemic areas, but involved relatively short periods of exposure (2–4 weeks) and malaria strains that are not as drug resistant as those currently existing in South East Asia.[6] There are reasons to hope that newer drugs and drug combinations such as WR 238605 and atovaquone with proguanil will be more effective prophylactics, but until they are available we are dependent on doxycycline or mefloquine.

Physicians must therefore be urged to fall back on the basics of clinical medicine when faced with a long-term visitor to Southeast Asia. Take a detailed history from the patient to estimate actual risk. Examine the patient carefully for diseases that would complicate antimalarial drug usage, such as ulcers or cardiac dysrhythmias. Explain any drug regimen carefully. Careful explanation is the single best way to ensure the patient will actually take the drug. Arrange medical care such that the patient knows where to go if problems are experienced, particularly fever after returning home.

For those of you interested in malaria, do not despair. Although the future drug possibilities are not overwhelming, progress is being made. For those of

you interested in drugs, keep working, we will certainly have malaria to deal with for a very long time. For the primary physicians, remember to explain malaria and individualize the preventive measures for each patient because the multifaceted problem of malaria in travelers no longer falls into only a few categories.

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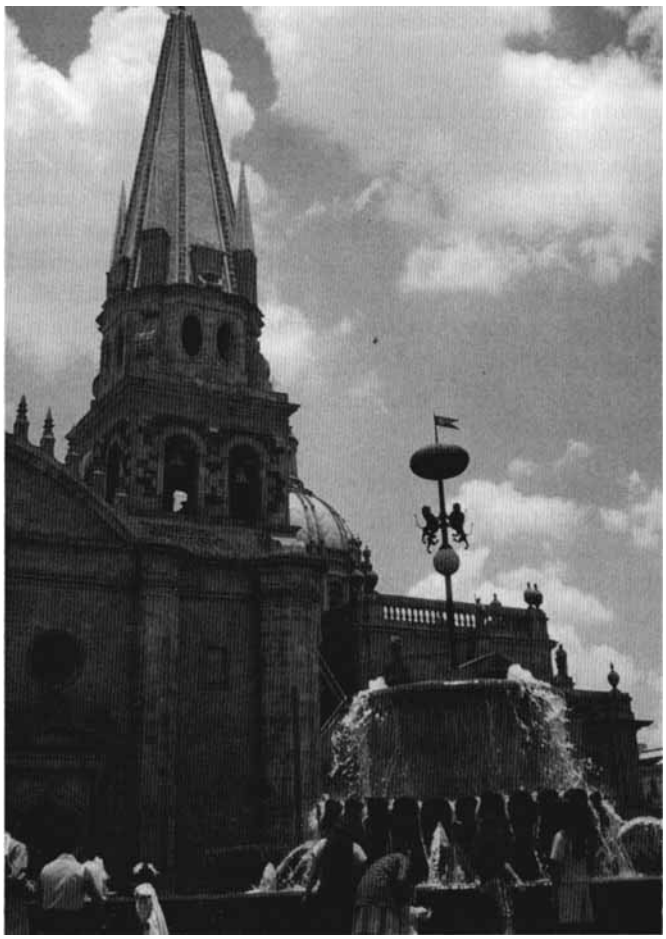

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