Malaria Prophylaxis: Taking Aim at Constantly Moving Targets

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Received March 12, 1992

The prevention of malaria infections is one of the most important functions that any clinician can perform for those traveling to tropical geographic regions where malaria risks are present. The prophylaxis question has become complicated by continued emergence of chloroquine-resistant strains of Plasmodium falciparum, the recent appearance of Plasmodium vivax resistance, and the availability of a wide choice of antimalarial pharmaceuticals. Chemoprophylaxis may produce different toxicities among various patient populations. With increasing numbers of women who travel during their professional lives, there are potential implications for using chemoprophylaxis during pregnancy. Children are unable to tolerate certain antimalarials because of toxicities unique for them. In some instances, the safest and most palatable formulations for children are not even available in the United States and must be purchased in Canada or elsewhere. Reliance upon chemoprophylaxis alone has proven to be increasingly futile. With the introduction of new repellent formulations and nontoxic insecticides for use on clothing or bed netting, there are non-pharmacologic adjunctive measures which can now be considered first-line for the prevention of malaria infections.

The prevention of malaria infections caused by one of the four known species of human plasmodia is based upon an understanding of the natural history of infection in both the mosquito vector and the human host. Malaria is transmitted to humans by the bite of an infected female anopheline mosquito, which utilizes a blood meal in the development of its eggs. Infective sporozoites, which the mosquito introduces into the host during biting, circulate in the peripheral blood for a period of only minutes before infecting the human liver. No clinical disease is evident at this stage of infection. Once merozoites have developed and are released from the liver into the circulation, they infect erythrocytes. The development of the asexual malaria parasites within erythrocytes ultimately leads to the destruction of infected erythrocytes and the release of additional infective merozoites. Some erythrocytic forms of the malaria parasite are destined to become sexual forms, either microgametocytes or macrogametocytes. They will continue the malaria cycle if they infect feeding mosquitoes in which sexual reproduction can continue, ultimately leading to the production of additional sporozoites to cause future human infections.

ADJUNCTIVE MEASURES FOR THE PREVENTION OF MALARIA: ALTERNATIVES TO CHEMOPROPHYLAXIS

During the past 50 years, since the discovery of chloroquine, if a physician were preparing travelers entering malarious areas, considerable emphasis would have

Abbreviations: CRPF: chloroquine-resistant P. falciparum DEET: N,N-diethyl-m-toluamide G6PD: glucose-6-phosphate dehydrogenase IC50: 50 percent effective dose UVA: long-range ultraviolet light

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been placed on the prevention of clinical disease, as opposed to the prevention of human infection. The latter can only be accomplished by controlling mosquito populations and their contact with humans. Chemoprophylaxis, as currently advocated, does not affect sporozoites and does not prevent malaria infections; it does stop the replication of malarial parasites in liver or erythrocytes [1]. Prophylactic agents, which primarily affect the erythrocytic stages and prevent clinical disease, are called suppressive. Those which affect liver forms and prevent release into the circulation are known as causal prophylactics.

There were many social and economic factors contributing to such a pharmaceutical approach, including the cost of spraying programs and the environmental toxicity associated with the use of insecticides. In addition, by the 1940s, U.S. research on antimalarial drugs was intensified due to the ongoing war with Japan in the Pacific. One derivative of the 4-aminoquinolones, SN 7618, was found to be both safe and extremely active against all species of human malaria [2]. This agent became known to a generation of physicians as chloroquine, and it had a very long period of clinical usefulness. To some extent, it still is very useful.

By the early 1960s, chloroquine use was becoming quite extensive, and the International Cooperation Administration was purchasing nearly 200,000 pounds of powdered chloroquine for a single medicated salt program to prevent malaria in Brazil. Over 88,000,000 tablets of chloroquine diphosphate were purchased for therapy in Brazil during one year alone [2]. With such intensive and widespread use of chloroquine, it was not surprising that chloroquine resistance emerged during the following decades, although the mechanism of resistance and its emergence were not really understood. This pattern of initial enthusiasm for antimalarial agents, followed by their extensive use, and the gradual loss of prophylactic efficacy due to the emergence of drug-resistant malaria strains has been repeated with other antimalarial agents. The problem continues to spread worldwide; therefore, we begin our discussion of malaria prophylaxis with a consideration of barrier methods for the prevention of contact between mosquito vectors and humans. The clear aim is effectively to prevent human malaria infections, not only disease, thereby reducing the need to rely only upon chemoprophylaxis.

Mosquitoes which transmit malaria often bite at dusk. It is best to wear long-sleeved shirts and long pants when outdoors at such times in order to prevent mosquito bites. There are several agents which are considered fairly useful topical insect repellents [3]. Out of this array of compounds, one of the most effective and readily available agents is N, N-diethyl-m-toluamide, or DEET. There are many commercial formulations, some of which contain nearly 100 percent DEET [3], but there is a price to be paid if they are misused. Focal allergic reactions, blisters, ulcerations, and skin necrosis have been reported. About 10 to 15 percent of a dose applied to the skin is absorbed and excreted in the urine. Toxic encephalopathy occurred in children who were sprayed repeatedly with 10–15 percent DEET preparations over periods from days to months, and one eight-year-old child has experienced seizures while using 100 percent DEET [4]. This repellent is quite useful, however, and it is now available as a one-ounce cream in a micronized encapsulated form and 35 percent concentration, which apparently provides protection for up to 12 hours following application (Ultrathon, Sports Products, 3M, St. Paul, MN). In this physical form, evaporation is diminished. Since less frequent applications are effective, the possibility of toxic reactions is likely to be diminished.
DEET can also be applied to clothing rather than to skin and offers protection without intense skin exposure; however, there are better alternatives for treating both clothing and bed netting.

Permethrin is a nontoxic, odorless pesticide, which is somewhat resistant to light, heat, and water immersion [4]. It is available as a spray or solution (Travel Medicine Inc, Northampton, MA; telephone: 800-872-8633) and can be used to impregnate bed nets or clothing. It apparently binds tightly to fabrics and lasts through several washings. Clinical trials in tropical areas of east Africa have shown permethrin-impregnated bed nets and curtains to be quite effective in village-wide malaria prevention programs [5]. Mosquito nets are available in several lightweight models with convenient carrying cases, in either free-standing or hanging models for one or two beds. The netting fabric should also be treated with about two ounces of permethrin. To reiterate, permethrin is an insecticide and not simply a mosquito repellent, thus offering considerable additional protection when used in conjunction with bed nets and topical repellents such as DEET.

Pyrethrum is a nontoxic natural derivative of the chrysanthemum flower. As an alternative to DEET, pyrethrum-containing sprays and mosquito coils can be used for children’s sleeping quarters in order to diminish mosquito exposure at night. Each of these preventive measures should be carefully considered and incorporated into any plan for the prevention of malaria before attempting to utilize pharmaceutical agents to which Plasmodium species are becoming increasingly resistant [6].

PHARMACEUTICAL AGENTS FOR PREVENTION OF MALARIA

Chloroquine Salts and Amodiaquine

For chemoprophylaxis against *P. vivax*, *P. ovale*, *P. malariae*, and chloroquine-sensitive strains of *P. falciparum*, chloroquine phosphate is still a safe and useful suppressive drug. Because of its bitter taste, it is often prescribed as an enteric-coated tablet (Aralen®, Winthrop), containing 300 mg of chloroquine base as 500 mg of the salt. Prophylaxis is usually initiated one week before reaching a malarious region. It is continued for four weeks after leaving the malarious area. The 50 percent effective dose (IC₅₀) for chloroquine is analogous to the minimum inhibitory concentration used to describe the activity of antibacterial agents. Chloroquine’s IC₅₀’s are in the range of 2 to 32 nM for chloroquine-susceptible strains of *P. falciparum* [7]. Chloroquine reaches serum levels of about 50 to 100 nM, with a half-life of about 6–13 days; hence it is quite acceptable as a weekly prophylactic agent. Adverse chloroquine effects are not usually a serious problem but do include pruritus, headache, gastrointestinal symptoms, and fatigue. Because of chloroquine’s affinity for melanin in tissues, the possibility of retinopathy is often a point of concern. Retinopathy is not associated with routine short-term chloroquine prophylaxis given on a weekly basis, resulting in total doses of far less than 100 grams. It is thought that chloroquine may exacerbate psoriasis, but there are little data indicating that this reaction is a significant problem. Since patients who are HIV-infected do have a higher incidence and severity of psoriasis, this result could be a potential problem to watch for when using chloroquine in this patient population. Chloroquine is known to interfere with the antibody responses to human diploid cell rabies vaccine, but it does not appear to interfere with the response to yellow fever vaccine [8]. Chloroquine is safe for malaria prophylaxis during pregnancy, but the spread of
chloroquine-resistant *P. falciparum* (CRF), and the recent appearance of chloroquine-resistant *P. vivax* in Iryan Jaya (Indonesian New Guinea) will surely diminish its reliability [9]. This development is unfortunate, given the lack of a suitable alternative agent for use during pregnancy in chloroquine-resistant malaria regions. Although amodiaquine has greater activity than chloroquine against some strains of *P. falciparum* with low-level chloroquine resistance, it is no longer recommended as an alternative agent to chloroquine because of reported cases of hepatitis and agranulocytosis [6].

**Mefloquine**

The antimalarial agent which has largely replaced chloroquine as a suppressive agent in areas where chloroquine resistance has been problematic is the quinoline methanol, mefloquine (Lariam®), which is somewhat similar in structure to quinidine and quinine. Mefloquine has a half-life of about 17 to 22 days, an advantage for purposes of chemoprophylaxis. This period is even longer than chloroquine’s, but not long enough for it to be used on an every-other-week basis. When alternate-week prophylaxis was attempted in Peace Corps volunteers working in west Africa, prophylaxis failures occurred during the second week [10]. The currently accepted prophylactic regimen is 250 mg weekly for adults, beginning one week before and continuing until four weeks after leaving a malarious region. Adverse effects are dose-related and are largely associated with gastrointestinal disturbances and dizziness. These effects appear to be pronounced in children. Splitting the weekly dose into two doses may help to diminish the gastrointestinal effects for both adults and children. Fears regarding possible neuropsychiatric disturbances in patients taking this agent for prophylaxis have not materialized. Mefloquine should not be given to patients who are receiving beta blockers or calcium channel antagonists because mefloquine has been associated occasionally with both sinus bradycardia and prolongation of the Q-T interval. The drug had appeared safe for use during pregnancy, but it is not approved for such purpose. At present, mefloquine is actually placed in FDA Pregnancy Category C, on the basis of embryotoxic and teratogenic effects. Use during pregnancy has been associated with reduced fetal growth and cleft palate [11]. Women with childbearing potential should be advised to use contraception both while taking mefloquine prophylaxis and for two months after their last doses.

**Sulfadoxine/Pyrimethamine**

In areas where CRF is endemic, Fansidar® (500 mg sulfadoxine and 25 mg of pyrimethamine) had been used for presumptive treatment of a febrile illness thought to represent malaria. The combination had also been used as part of a weekly regimen of prophylaxis during prolonged exposure to CRF. Resistance appeared in east Africa and rural Thailand, but one factor limiting its use was the appearance of severe adverse cutaneous reactions, including toxic epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome, from which several deaths resulted [6]. Patients should be instructed to stop this medication and seek medical attention if they experience a cutaneous reaction while taking it. The need for medical attention is also based upon the assumption that another agent will be substituted for prophylaxis if the reaction is found to be potentially serious. Sulfadoxine competes with bilirubin and can exacerbate neonatal jaundice. Pyrimethamine has not been
shown to be a human teratogen, but it is teratogenic in animals. We would still not recommend the use of this combination during the third trimester of pregnancy.

**Doxycycline**

In areas such as Thailand, where there is now considerable resistance to many antimalarials, including mefloquine, the tetracyclines have gained an important role in malaria prophylaxis. Recall that tetracyclines, proguanil, and pyrimethamine are examples of causal prophylactic drugs, which have activity against the exoerythrocytic hepatic forms [6], in addition to suppressing symptoms via their action on erythrocytic asexual forms of the parasite. Doxycycline (100 mg/day) can be used in geographic areas where there is CRPF risk, or for patients who are allergic to sulfa drugs. The problems of both Fansidar® resistance and emerging mefloquine resistance, particularly in Thailand, can be approached by using daily doxycycline prophylaxis, while in such a region and for four additional weeks after leaving. Adverse effects include photosensitivity reactions. These can be prevented by using a broad-spectrum sunscreen (e.g., Photoplex®) to block those ultraviolet light wavelengths (UVA) responsible for photosensitivity reactions. Women should carry an antifungal preparation for the treatment of possible candida vaginitis secondary to tetracycline use. Tetracyclines are not to be used in children less than eight years old since they inhibit bone growth and may cause discoloration and dysplasia of teeth. Tetracyclines are also contraindicated during pregnancy because their effects on the fetus are similar to their effects in young children.

**Proguanil (Chloroguanide)**

Proguanil (Paludrine®) is a biguanide agent which, like pyrimethamine, is a dihydrofolate reductase inhibitor. Most experience with the agent was with doses of 100 mg/day, and the recommended daily dose is 200 mg/day. Although proguanil is effective in some geographic areas, it is not very useful in others, such as Papua New Guinea or Thailand [6]. Proguanil is continued for four weeks after leaving a malarious region, and it appears to be safe during pregnancy, although not much information is available for the dose of 200 mg/day. Proguanil is not available in the United States and must be purchased in Canada or elsewhere.

**TERMINAL PROPHYLAXIS WITH PRIMAQUINE**

Both *P. vivax* and *P. ovale* produce latent infections in the human liver. If not eradicated, these latent forms or hypnozoites may cause relapsing infections months to years after a traveler leaves a malarious region. To prevent such relapses from occurring, the physician administers the 8-aminoquinolone, primaquine, 15 mg base orally for 14 days following the final four weeks of chloroquine prophylaxis. Patients with the severe forms of glucose-6-phosphate dehydrogenase (G6PD) deficiency can develop hemolysis while taking primaquine, and patients with the severe Mediterranean form of the deficiency should not be given this agent. If malaria relapses do occur in such patients, they can be treated with chloroquine. Occasionally, primaquine use may be associated with some nausea, vomiting, or headache. For women who are pregnant, chloroquine should be used each week, when exposure to *P. vivax* or *P. ovale* occurs; it can be continued throughout pregnancy and primaquine use delayed until after delivery. Neither terminal prophylaxis nor so-called radical cure with primaquine are indicated during pregnancy. The effects of this agent on the
fetus are not known, and there is the theoretical possibility that a G6PD-deficient fetus could experience an episode of hemolysis in utero because the drug may be passed transplacentally.

We reported a failure of primaquine to prevent a relapse of *P. ovale* in a Yale physician who acquired a mixed malaria infection while traveling in Kenya [12]. It is not known whether the standard 15 mg (base) dosage regimen of 14 days was too little for a 100 kg (220-pound) man, or whether *P. ovale* is relatively more resistant than *P. vivax* to this agent. For this patient, a 30 mg dose regimen seems to have ended his problem with relapses; however, we recently had a similar experience with an average-sized student who returned from Borneo in August of 1991. After receiving appropriate mefloquine prophylaxis, she required treatment for what appeared to be vivax malaria seven weeks after completing her course of mefloquine prophylaxis. Because of manufacturing problems associated with the unavailability of primaquine in 1991, she had not received any primaquine nor any information regarding its use. It was then administered in early November, in a dose of 15 mg base per day for two weeks, only to have her present with a relapse during her Christmas holidays while visiting family in Virginia. Like our physician-patient, she also required a course of 30 mg per day in an attempt to prevent further relapses. This development is not an unusual occurrence [13], and primaquine will probably be replaced by a more efficacious agent in the near future.

**PROPHYLAXIS AND COMPLIANCE IN CHILDREN**

Mothers who are breastfeeding and taking any antimalarial agents should be made aware that insufficient drug is transferred to the infant in breast milk for it to serve as an effective prophylactic agent in a child. Infants require their own regimen of antimalarial prophylaxis. To prevent malaria in children, the use of barrier methods should be emphasized, avoiding exclusive reliance upon chemoprophylaxis, since there are always issues of compliance and efficacy when using pharmaceutical agents in children. To increase compliance with the use of chloroquine, parents should purchase chloroquine suspension (Nivaquine) overseas, since it is not available in the United States. If the parent is unable to obtain it, Plaquenil® (hydroxychloroquine) can be purchased in the United States. When pulverized and mixed with food, it is less bitter and is more tolerated. Regimens for prophylaxis based upon use of chloroquine are still useful in Haiti, Central America, and the Middle East. Resistance of *P. vivax* to chloroquine is emerging in Iryan Jaya [9] and may be problematic for other malaria areas in the future. Mefloquine is a useful agent in children who are more than 15 kg (33 pounds) in weight. If smaller, they may not tolerate the drug because of nausea, vomiting, or dizziness. There are no available data on mefloquine’s safety for children under this size which would allow its use. Because resistance to mefloquine has already emerged in Thailand, it is no longer relied upon in that area. Adults may use a daily regimen of doxycycline, which is contraindicated in children under the age of eight. It has been suggested that the combination of proguaanil and sulfisoxazole (sulfaphurazole) could provide greater than 95 percent protection against falciparum malaria in such areas, with 100 percent efficacy against vivax malaria [14]. After leaving geographic regions where vivax malaria occurs, both children and adults should be given terminal prophylaxis with primaquine after appropriate screening for any of the severe forms of G6PD deficiency. Keep all
antimalarials, particularly chloroquine, stored in childproof containers, as overdosage can easily result in a fatality.

Pregnant women are at greater risk of causing fetal growth retardation or fetal loss, if clinical malaria occurs during pregnancy. As a general rule, travel to areas where chloroquine-resistant malaria is endemic should be avoided by pregnant women [15]; there are too few pharmacological options to offer them. The best alternatives to chloroquine are physical methods for the prevention of mosquito contact, including long-sleeved clothing treated with permethrin-containing insecticides and the repellent, DEET. Primaquine should not be used during pregnancy for terminal prophylaxis, but chloroquine can be continued during pregnancy until delivery, after which primaquine may be administered. Alternatives to chloroquine during pregnancy include proguanil, which is not effective in some areas of west Africa, Thailand, and Papua, New Guinea. Fansidar® can be carried for presumptive treatment of febrile episodes potentially due to falciparum malaria. The risks appear to be minimal in relation to the risks associated with the occurrence of falciparum malaria during pregnancy. The reader is referred to a complete discussion of such issues during pregnancy and a review of toxicities associated with antimalarial medications during pregnancy [15].

Malaria prophylaxis has come full circle. With an imperfect understanding of both the transmission and pathogenesis of malaria infections in the past, it was still possible to reduce malaria transmission by draining swamps and removing breeding sites for anopheline mosquitoes. The advent of chemoprophylaxis with the agents described above has not solved the problem, as the emergence of resistance to antimalarials has shown us. For a listing of currently recommended dosing schedules for the antimalarials described here, the reader is referred to the most recent issue of The Medical Letter, which appears every other year in March [17]. This publication includes the most recent recommendations on the use of antimalarial agents for both adults and children. When advising those who are living, working, or vacationing in malarious regions, however, physicians who staff travelers’ clinics will now emphasize some of the newest developments in the use of barrier methods for the prevention of malaria infections [15,16]. Ultimately, reduction in contact between humans and infected anopheline mosquitoes will be one key to malaria prevention.

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