MINIREVIEWS

Antimalarial Agents: Specific Chemoprophylaxis Regimens

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In recent minireviews (21, 32), we examined mechanisms of antimalarial action and resistance. Here we examine regimens which are recommended or are being studied for the prevention (chemoprophylaxis) of malaria. We begin with an examination of in vitro and in vivo correlates as a bridge between the laboratory and clinical aspects of malaria.

IN VITRO AND IN VIVO CORRELATES

In vitro susceptibility testing and clinical outcome. The correlations between in vitro susceptibility testing and clinical outcome are imprecise. They are more qualitative than quantitative. Thus, there are no ranges of 50% effective doses or inhibitory concentrations for chloroquine, mefloquine, or other antimalarial agents which are clearly associated with the failure or success of treatment in vivo. Nevertheless, for isolates which are susceptible in vivo to chloroquine, 50% effective doses or MICs are generally lower than those for isolates which are resistant (2 to 32 versus 40 to 300 nM) (9, 12-14, 18, 20).

Partitioning of chloroquine in vivo. The precise in vivo partitioning of chloroquine is unknown. However, studies by several investigators indicate that chloroquine is concentrated primarily within the acid intravesicular compartment of mammalian cells (26, 30). Pharmacokinetic studies in persons without malaria indicate that chloroquine levels in serum are 50 to 100 nM in persons taking routine chemoprophylaxis (2, 11, 15) and peak at ≤ 1 to 2 μ M in persons receiving a treatment course of chloroquine (29, 38). Based on the chloroquine concentrations necessary to inhibit parasite growth in vitro, the levels of chloroquine achieved in serum should be more than sufficient to inhibit and kill susceptible parasites during chemoprophylaxis and treatment. In contrast, they should not inhibit resistant parasites during chemoprophylaxis and should inhibit them only transiently during treatment.

Impact of chloroquine efflux in vivo. Chloroquine efflux from the resistant parasite has been demonstrated only recently (21), and it is not yet clear how it functions (e.g., whether it saturates) in vivo. However, recent in vitro studies indicate that the rate of chloroquine efflux (the initial release half-life of chloroquine from the resistant parasite) does not change over a 10,000-fold range of extracellular chloroquine concentrations (D. J. Krogstad, I. Y. Gluzman, and P. H. Schlesinger, unpublished observations). These observations suggest that the extracellular chloroquine concentrations achieved in serum are unlikely to overwhelm this mechanism in vivo.

CHEMOPROPHYLAXIS OF MALARIA

Travelers can decrease their risk of malaria by taking antimalarial chemoprophylaxis (Table 1), although no one regimen is ideal for travelers to all malarious areas (8, 33). Important considerations in selecting a regimen include the geographic areas to be visited, the prevalence of chloroquine-resistant *Plasmodium falciparum* (CRPF) infection in those areas, the time of year, and extent of exposure (4, 5, 7, 40).

***Plasmodium vivax*, *P. ovale*, *P. malariae*, and chloroquine-susceptible *P. falciparum*.** Chloroquine is the mainstay of antimalarial chemoprophylaxis and should be taken by virtually all travelers at risk of acquiring malaria. *P. vivax*, *P. ovale*, and *P. malariae* are all chloroquine susceptible. Chloroquine chemoprophylaxis prevents infections caused by these parasites and by chloroquine-susceptible *P. falciparum*. Despite the in vitro data presented above (in the section on susceptibility testing), a number of investigators believe that chloroquine chemoprophylaxis may reduce the severity of infections caused by CRPF.

Chloroquine chemoprophylaxis is taken once a week, beginning 1 week before and continuing 6 weeks after the last exposure in an endemic area (500 mg of chloroquine phosphate or 300 mg of chloroquine base for adults). The efficacy of weekly chloroquine chemoprophylaxis is consistent with its long serum half-life (approximately 6 to 13 days) (8). Amodiaquine has greater activity than chloroquine against some *P. falciparum* isolates with low-level chloroquine resistance (34, 36) and was recommended previously for chemoprophylaxis. However, amodiaquine recently has been found to cause severe hepatitis (22, 25) and agranulocytosis (6, 10, 31) and therefore is no longer recommended for chemoprophylaxis.

CRPF. The chemoprophylaxis of CRPF infection is complex. Because the pyrimethamine-plus-sulfadoxine combination (Fansidar) may produce fatal reactions (erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis) (24), it is no longer recommended for routine chemoprophylaxis for travelers to areas with CRPF (4, 5). The U.S. Public Health Service (Centers for Disease Control) recommends that travelers to areas with CRPF take chloroquine chemoprophylaxis weekly and carry a therapeutic dose of pyrimethamine-sulfadoxine (three tablets, each containing 25 mg of pyrimethamine and 500 mg of sulfadoxine) for presumptive treatment of febrile illness if professional medical care is not available.

Weekly chloroquine-plus-pyrimethamine-sulfadoxine chemoprophylaxis may be used for prolonged, extensive exposure in high-risk areas for CRPF when medical care is not available. However, failures of chloroquine-plus-pyrimethamine-sulfadoxine prophylaxis have been documented in

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TABLE 1. Chemoprophylaxis of malaria^a

Organism(s) and antimalarial agent	Regimen for:	
	Adults	Children
<i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> , and chloroquine-susceptible <i>P. falciparum</i> : chloroquine phosphate (Aralen)	300 mg of base (500 mg of chloroquine phosphate) per wk	5 mg of base per kg per wk, up to 300 mg of base
CRPF: chloroquine (as above) plus one of the following: Doxycycline (Vibramycin) ^b	100 mg/day	Not recommended for children less than 8 yr old because of toxicity for bones and teeth
Proguanil (Paludrine)	200 mg/day	<2 yr, 50 mg/day; 2–6 yr, 100 mg/day; 7–10 yr, 150 mg/day; >10 yr, 200 mg/day
Pyrimethamine-sulfadoxine (Fansidar)	1 Tablet (25 mg of pyrimethamine + 500 mg of sulfadoxine) per wk	2–11 mo, 1/8 tablet/wk; 1–3 yr, 1/4 tablet/wk; 4–8 yr, 1/2 tablet/wk; 9–14 yr, 3/4 tablet/wk; >14 yr, 1 tablet/wk
Late relapse caused by <i>P. vivax</i> or <i>P. ovale</i> : primaquine phosphate	15 mg of base (26.3 mg of salt) per day for 14 days with the last 2 wk of chloroquine chemoprophylaxis	0.3 mg of base per kg up to a maximum of 15 mg of base

^a Chemoprophylaxis should be begun 1 week before departure. This permits one to determine whether the patient will tolerate the drug(s) and to be sure that he will not require a change in his regimen. Chemoprophylaxis should be continued for 4 to 6 weeks after leaving the endemic area to protect against symptomatic parasitemia from infections acquired shortly before departure (6 weeks for chloroquine; 4 weeks for doxycycline, proguanil, pyrimethamine-sulfadoxine). Doxycycline plus chloroquine has been used more extensively in Southeast Asia, whereas the proguanil-plus-chloroquine combination has been used more extensively in East Africa. Pyrimethamine-sulfadoxine plus chloroquine has been used in both Southeast Asia and Africa but has been associated with serious reactions (see the text for details; 24).

^b A number of investigators now suggest using doxycycline without chloroquine for chemoprophylaxis of CRPF.

East Africa (23), and resistance to these drugs is widespread in rural Thailand.

There are no well-established alternatives to pyrimethamine-sulfadoxine for the chemoprophylaxis of CRPF. Doxycycline and proguanil (Paludrine) are potential alternatives in areas with chloroquine and pyrimethamine-sulfadoxine resistance, although the clinical experience with these compounds is much less extensive than that with chloroquine, pyrimethamine-sulfadoxine, or the chloroquine-plus-pyrimethamine-sulfadoxine combination (27). Potential regimens include either daily doxycycline (100 mg/day) or daily proguanil (200 mg/day) to prevent CRPF plus weekly chloroquine to prevent infections caused by chloroquine-susceptible plasmodia (1, 28, 35). Unfortunately, the value of doxycycline is limited by a number of important toxicities. It is contraindicated in pregnant women and young children because of its effects on growing bones and teeth (4), it produces vaginitis frequently, and it produces photosensitivity reactions (3). Although proguanil has been used for many years and is thought to be safe (17), most of the previous experience with this drug has been at a lower daily dose (100 rather than 200 mg/day). The efficacy of proguanil appears to vary in different areas of the world. For instance, it is not effective for the chemoprophylaxis of CRPF in Papua New Guinea (16) or Thailand. Proguanil is not available in the United States but is available in Europe and throughout the developing world.

When mefloquine is approved by the U.S. Food and Drug Administration, it will also be an alternative for the chemoprophylaxis of CRPF. The dose recommended is expected to be 250 mg of mefloquine base weekly for adults (4 mg of base per kg for children). Because of its long half-life (17 to 22 days), it should be possible to discontinue mefloquine chemoprophylaxis when leaving the endemic area or shortly thereafter.

Prevention of relapsing malaria with primaquine. Primaquine is used to prevent relapse of *P. vivax* or *P. ovale* infection after extensive exposures in areas endemic for these species. It prevents relapse by eradicating latent exoerythrocytic forms in the liver. These latent forms (hypnozoites) do not exist in *P. falciparum* or *P. malariae* infection. Because hypnozoites result from infection of the liver by sporozoites, they do not form in blood-induced infections caused by any malarial species. Thus, one does not need to give primaquine for transfusion malaria or for malaria acquired by addicts to intravenous drugs, even if the species is *P. vivax* or *P. ovale*.

Primaquine is not used routinely for postexposure chemoprophylaxis because of its side effects. These include hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as well as nausea, vomiting, and headache (37). African patients with G6PD deficiency often tolerate primaquine without significant hemolysis and are often given primaquine without prior testing for G6PD deficiency. However, most physicians in the developed world test for G6PD deficiency before administering primaquine. This is because treatment with primaquine is not emergent (hypnozoites in the liver do not produce clinical illness until they mature and release merozoites) and because patients with the Mediterranean form of G6PD deficiency may have severe hemolysis with primaquine. Patients with severe G6PD deficiency should not receive primaquine (37). They should be treated with chloroquine for each relapse (25 mg of chloroquine base per kg [body weight] over a 3-day period; 19).

When primaquine is used, 15 mg of primaquine base is given daily for 14 days with the last 2 weeks of chloroquine chemoprophylaxis. If relapse occurs despite chemoprophylaxis with primaquine, the patient should receive a therapeutic

tic course of chloroquine followed by a second course of primaquine for 3 to 4 weeks (with weekly chloroquine).

Pregnant women should avoid taking primaquine until after delivery because its effects on the fetus are unknown. The most reasonable strategy in a pregnant woman with *P. vivax* or *P. ovale* infection is to continue weekly chloroquine chemoprophylaxis after treatment until delivery.

Chemoprophylaxis for pregnant women. Chloroquine chemoprophylaxis is known to be safe (39) and should be given to pregnant women traveling to malarious areas. However, none of the regimens used for the chemoprophylaxis of CRPF infection has been shown to be safe in pregnancy (19). Nonimmune pregnant women planning travel to areas with CRPF should be advised about the risks of malaria in pregnancy and of chemoprophylaxis with drugs that have not been shown to be safe in pregnancy. They should consider deferring such travel until after delivery in order to reduce these risks.

Postpartum chemoprophylaxis and the newborn. Although antimalarial agents taken by the mother cross into breast milk, the concentrations achieved are poorly defined and have not been shown to prevent malaria in the newborn. For this reason, infants born in malarious areas should receive antimalarial chemoprophylaxis.

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