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Malaria Chemoprophylaxis for the International Traveler, Current Options and Future Possibilities

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1. Introduction

Malaria remains the most important parasitic disease in the world, causing approximately 250 million infections annually and one million deaths, mostly in African children. International travelers are at risk of developing malaria when visiting endemic regions, and account for an estimated 30,000 cases of malaria annually (World Health Organization, 2011). The parasite is transmitted by the female Anopheles mosquito and is caused by four protozoa of the *Plasmodium* genus *(P. falciparum, P. vivax, P. ovale* and *P. malaria)*. *P. falciparum* causes the most significant disease burden with the highest morbidity and mortality. In addition to mosquito control and avoidance measures, chemoprophylaxis remains a critical component for preventing malaria infection in non-immune travelers.

Addressing malaria chemoprophylaxis for the international traveler can be challenging. In addition to patient-specific factors, the provider must consider a wide array of other variables, such as the predicted risk of malaria associated with the destination, type and duration of exposure during the trip as well, as the profile of the drug being prescribed. Seasonal, geographic, and climate are among the environmental variables that should be addressed to appreciate risk of malaria transmission. There can be upwards of a 200-fold difference in relative risk of contracting malaria depending on geographic variables for the international traveler, with sub-Saharan Africa conferring the greatest risk (Leder et al., 2004; Freedman, 2008). The traveler's accommodations, anticipated understanding and adherence to mosquito avoidance and control measures, chemoprophylaxis and access to appropriate medical care contribute to the risk of morbidity and mortality associated with malaria.

Patient-specific variables can also present challenges to the provider. Pregnant, nursing and pediatric travelers present unique considerations when determining the most appropriate chemoprophylactic regimen. Pregnant patients incur a much higher risk of mortality and morbidity from malaria than non-pregnant travelers, and require extensive counselling on the risks and benefits of proposed travel to areas at risk of transmission. Emerging parasite drug resistance patterns, side-effect profiles, both long and short term, contraindications and poor adherence are additional challenges that need to be considered when selecting an appropriate antimalarial chemoprophylactic agent. In addition, how to address chemoprophylaxis in long-term travelers, generally defined as travel greater than six-

months in duration, can be very difficult as consensus guidelines in this population are not available (Chen et al., 2006).

It has been over ten years since the U.S. Food and Drug Administration has approved an antimalarial chemoprophylactic drug. Lack of market incentive, increasing difficulty in the design and execution of clinical trials, as well as the changing ethical environment after Declaration of Helsinki 2000 have contributed to the lag in continued development for the malaria chemoprophylaxis indication (Dow et al., 2008).

2. Education

Before travel, counseling the individual on the specific risks in the areas they may be visiting is an essential part of trip preparation. When counseling the traveler prior to visiting an endemic area, they must be made aware of the route of transmission of malaria, associated symptoms, variable incubation periods prior to symptom onset, when to seek medical aid, and the risks of contracting the disease, including death, especially in high-risk populations. They need to be aware that recent immigrants to non-malaria endemic areas returning to their home of origin to visit friends and relatives (VFR's) are at high risk for contracting malaria as acquired immunity is not long lasting (Centers for Disease Control and Prevention, 2012). Travelers should be counseled on proper personal protective measures including mosquito bite avoidance, especially during the peak transmission periods of evening and nighttime hours, mechanical and chemical barrier protection, vector control, and the appropriate use and importance of chemoprophylaxis.

Malaria can be effectively treated if suspected and recognized early and appropriate medical intervention is made within a timely manner. Time to symptom onset from initial exposure can vary, ranging as early as 7 days following a mosquito bite to several months or greater following departure from an endemic region. The diagnosis of malaria is a medical emergency since time to definitive treatment is a critical factor in determining clinical outcome. For these reasons, travelers should be counseled to seek medical care as soon as possible if they have any symptoms that may be related to malaria. The clinical presentation of malaria consists of a nonspecific, flu-like illness manifested by fever, chills, malaise, anorexia and headache. In cases of severe illness, altered mental status, seizures, respiratory disease (ARDS) and coma may be present (CDC, 2012).

Availability of medical care while traveling should be explored prior to travel. There may be rare instances where the chemoprophylaxis regimen is suboptimal or the traveler does not agree to medically advised chemoprophylaxis. In cases when the traveler develops clinical symptoms consistent with malaria and does not have timely access to medical care and definitive parasitological diagnosis, presumptive, self-administered therapy may be considered (WHO, 2010; CDC, 2012). When prescribing presumptive self-treatment, the CDC recommends a consecutive 3-day course of either atovaquone-proquanil or artemether-lumefantrine. One should never use the same drug for treatment that had been prescribed for prophylaxis. It should be stressed to the traveler that even though presumptive treatment may be available, they should seek medical care as soon as possible.

3. Personal protective measures

Several measures can be taken by the traveler while in endemic areas to reduce the risk of mosquito bites, thus reducing the risk of contracting malaria. The *Anopheles* mosquito only

feeds at night, making the hours between dusk and dawn those that the traveler must be most vigilant for vector avoidance and mosquito control measures. Staying indoors, sleeping in screened-structures, and using mosquito nets during peak feeding times are all effective and relatively simple ways to reduce transmission of malaria. Other protective measures including clothing that minimizes exposed skin, eliminating mosquito breeding sites, and using appropriate repellents/insecticides on skin and clothing, should be discussed with the traveler as well (Chen et al., 2006; CDC, 2012).

A systematic literature review concluded that environmental management programs were highly effective at reducing the morbidity and mortality associated with malaria, and if educated properly travelers can reduce their risk significantly through these personal and environmental protective measures (Keiser et al., 2005).

Insecticides such as permethrin can be used as a spray to kill mosquitoes on contact, or can be used to impregnate clothes and mosquito nets for long-term protection. A 2003 randomized-controlled trial in sub-Saharan Africa showed a reduction in all-cause child mortality by 15-33% with the use of permethrin treated bed nets and curtains, and a 1995 study of permethrin impregnated uniforms in Columbian soldiers showed a decrease in incidence of malaria from 14% to 3% (Phillips-Howard & Nahlen et al., 2003; Soto & Medina et al., 1995), indicating mosquito avoidance and control measures can be highly effective in preventing malaria transmission.

Repellents prevent arthropod bites via alterations to sensorial organs. There are several different commercially available repellents including DEET (*N*,*N*-diethly-3-methyl-benzamide), picaridin (2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester), oil of lemon eucalyptus (*para*-menthane-3,8-diol), and IR3535 (3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester). The efficacy and duration of repellents vary considerably among products and species of mosquito (Zielinski-Gutierrez et al., 2012). Several studies have suggested DEET and picaridin to be the most efficacious and long lasting (Fradin & Day, 2002; Trigg, 1996; Govere et al., 2000; Badolo et al., 2004). Both DEET and picaridin demonstrate efficacy between five and seven hours after application, with variations in efficacy and duration of effectiveness related to repellent concentration, humidity, temperature, perspiration, exposure to water, and abrasion (Zielinski-Gutierrez et al., 2012). There seems to be a ceiling effect with DEET at concentrations above 50%, where higher concentrations do not offer additional benefit.

DEET, at concentrations up to 50%, can be used on children over two months of age. Children less than two months should be protected with a child carrier covered with a mosquito net. Beyond labeled precautions, the U.S. Environmental Protection Agency (EPA) and CDC do not recommend additional warnings for repellents in children > 2 months, pregnant or lactating women (Zielinski-Gutierrez et al., 2012). Like physical barriers, repellents and insecticides are only effective if used properly and consistently, thus ensuring the traveler is aware of proper use before departing is an essential part of pre-trip counseling.

4. Chemoprophylaxis

Educating travelers on the clinical indications, as well as proper use and risks of chemoprophylaxis is an important part of pre-travel counseling. Patients should be told of the options available for the area they are traveling based on CDC recommendations, and when clinically indicated, an appropriate chemoprophylaxis should be chosen and

prescribed based on the patient's medical history, tolerability of side effects, compliance, and known resistance in the area (Table 1). Resistance to antimalarial drugs is growing, and is a major public health concern (WHO, 2010). Resistance of *P. falciparum* to chloroquine, the most widely available and least expensive chemoprophylaxis agent, is now widespread, except in a few limited areas of the Caribbean, Central and South America, and a few countries in the Middle East. Resistance to mefloquine is spreading and has been confirmed in areas of SE Asia including along the borders of Burma and China, Laos and Burma, Thailand and Burma, Thailand and Cambodia, and in southern Vietnam (CDC, 2012).

4.1 Chloroquine

Chloroquine is a 4-aminoquinoline oral antimalarial agent first introduced in the 1940's. It has good bioavailability, is rapidly absorbed and appreciably concentrated in tissues such as the liver, spleen, and to a lesser extent in the CNS (WHO, 2010). Its plasmodicidal activity is thought to be related to its interaction with malarial DNA, specifically haem detoxification (Castelli et al., 2010; WHO, 2010). Chloroquine is dosed once weekly and is effective against the erythrocytic stages of sensitive plasmodium species.

Chloroquine has long shown its efficacy against malaria, and was a cornerstone of treatment until growing resistance became a problem in the 1980's (Castelli et al., 2010). *P. falciparum* resistance to chloroquine is widespread, thus making it an acceptable choice only in chloroquine sensitive areas. There is some evidence of mutations making non-falciparum strains resistant, with resistance of *P. vivax* to chloroquine reported in areas of Papua New Guinea, West Papua, Guyana, Vanuatu, Myanmar, Indonesia, and India (WHO, 2010; Kain et al., 2001; Davis et al., 2003).

Chloroquine has a generally mild side effect profile with the most common events being nausea, headache, blurred vision, insomnia, and pruritis (Castelli et al., 2010). Serious side effects, although rare, include myopathy, hepatitis, hearing loss, Stevens-Johnson Syndrome, seizures, and irreversible retinopathy (WHO, 2010). Retinopathy is usually seen after 100g cumulative dose, which is equivalent to what a long-term traveler may ingest in 5-6 years of weekly dosing (Chen et al., 2006). Chloroquine-induced retinopathy is rare in patients taking malaria prophylaxis and is more frequently seen in the higher doses administered for the treatment of rheumatoid arthritis (CDC, 2012). In a large (N=2701) trial of peace corps volunteers undergoing malaria prophylaxis it was found that chloroquine was better tolerated and had fewer serious side effects than mefloquine or doxycycline, however prophylaxis in general was not tolerated well with 9% reporting severe events and 23% at some point changing their prophylactic medication (Korhonen et al., 2007).

Chloroquine is considered safe for use in children and pregnancy, however strict adherence to weight-based dosing must be adhered to for children since serious adverse events have been reported in children receiving as little as 1 gram of chloroquine (Chen et al., 2006). While chloroquine is safe for breast-feeding mothers, the infant should receive separate prophylaxis as the amount of chloroquine secreted in breast milk is not sufficient for protection.

Chloroquine is available in 500mg tablets, which is equivalent to 300mg chloroquine base. Dosing is done weekly starting 2 weeks before travel into an endemic area and for 4 weeks after leaving the area. Pediatric dosing is 5mg/kg base, never to exceed adult dosing.

While generally considered a safe and efficacious drug, the growing resistance to chloroquine is making it a choice only available in limited areas of the world. However,

because it is one of two current drugs considered safe in pregnant women and children, and because it is fairly well tolerated, it will remain a viable choice for prophylaxis if resistance patterns are taken into account when prescribing.

4.2 Primaquine

Primaquine phosphate is an oral antimalarial agent first approved by the FDA in 1952. The mechanism of action is not well understood, but its plasmodicidal activity is thought to be related to disruption of the parasitic electron transport chain (Castelli et al., 2010). It has a short half-life of approximately seven hours, thus requiring daily dosing. Before the approval of primaquine, there was no available treatment of relapsing malaria because anti-malarial drugs available at the time were only effective against the erythrocytic stages of Plasmodium species (Shanks et al., 2001). Primaquine's approval was important because it is effective against both the erythrocytic and exoerythocytic stages of Plasmodium species, making it an effective choice for *P.vivax, P. ovale, or P. falciparum* (WHO, 2010; Shanks, Kain et al., 2001). However, it is only FDA-approved for the treatment of vivax malaria, but has long been used for treatment off-label for other species and is the drug of choice for terminal prophylaxis in travelers at risk for relapsing malaria (Castelli et al., 2010; Hill et al., 2006).

Multiple clinical trials have shown the efficacy of primaquine against both vivax and falciparum malaria (Shanks et al., 2001). In two placebo controlled trials on the island of New Guinea it was shown that primaquine had an efficacy of 93 - 95% against *P. falciparum* and 88 - 90% against *P. vivax* (Baird et al., 2001; Fryauff et al., 1995). In two placebo controlled trials done in Columbia good efficacy was also seen, with an overall efficacy of 89% against *P. falciparum* and 88% against *P. Vivax* (Soto et al., 1998, 1999). While good efficacy has been seen in the past, there is emerging evidence of increasing resistance to *P. Vivax* strains in some areas of Oceana, South East Asia, and South America (Baird, 2009).

Primaquine is a well-tolerated medication with the most common side effects being nausea, vomiting, and abdominal cramps (Fryauff et al., 1995). It was shown to have better tolerability than chloroquine in Irian Jaya transmigrates, and in a retrospective study of travelers to Ethiopia it had favorable tolerability compared to mefloquine and doxycycline (Schwartz & Regev-Yochay, 1999; Baird et al., 2001). Severe hemolytic anemia can occur in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and should be avoided in any patient with this enzymopathy. All patients taking primaquine should be evaluated for G6PD deficiency prior to receiving this drug (Hill et al., 2006).

Off-label dosing recommendations are 30mg base per day for 14 days for terminal prophylaxis, and 30mg per day 1-2 days before travel and continued for 7 days after travel for prophylaxis (CDC, 2012). It should be taken with food to limit side effects. Dosing for children is 0.5 mg/kg base per day. It has been shown safe in studies up to one year with no labeled restrictions on duration of use (Fryauff et al., 1995; Chen et al., 2006). Primaquine is contraindicated in pregnant women, making prevention or treatment of malaria in areas with *P.vivax* difficult in this population. If used as a primary prophylaxis, it negates the need for terminal prophylaxis, however, if another primary chemoprophylaxis is chosen, and relapsing malaria is a concern, it makes a good choice for terminal prophylaxis.

4.3 Mefloquine

Mefloquine hydrochloride is a methanol-quinoline oral antimalarial agent whose mechanism of action is not completely understood, but is thought to be similar to quinine

(Castelli et al., 2010). It acts as a blood schizonticide, making it highly effective against the erythrocytic stages of Plasmodium species, however it does not have any exoerythrocytic activity. Mefloquine has a long half-life, with the average being 21 days, thus only requiring once-weekly dosing. Mefloquine is effective against chloroquine resistant Plasmodium species, however there are some areas in SE Asia with known mefloquine resistance. Of note, mefloquine has been found to have serious neuropsychiatric adverse events, which limit its usefulness in certain populations (Castelli et al., 2010; Croft & Garner, 2008).

Mefloquine efficacy has been shown to be greater than 90% in multiple clinical trials (Kain, Shanks et al., 2001), the longest of which was in Peace-Corps volunteers in Africa during the early 1990's. In addition, a review of mefloquine trials found that it did prevent malaria in chloroquine resistant areas (Croft & Garner, 2000). Although an effective medication, the endemic risk of malaria, current resistance patterns, the drug's side effect profile and the patient's medical and psychiatric history should be carefully considered before prescribing mefloquine (Croft & Garner, 2000).

The mefloquine label lists many side effects, the most common of which are nausea, vomiting, diarrhea, and abdominal pain. However, it also states that mefloquine can cause serious mental problems including anxiety, paranoia, hallucinations, and suicidal thoughts. These psychiatric problems may lead to prophylaxis discontinuation, and should be considered when choosing the appropriate chemoprophylactic regimen. The high rate of side effects associated with mefloquine has been shown in several clinical trials including a randomized, double blind controlled study of 623 travelers. This study found that mefloquine had the highest rate of neuropsychiatric adverse events at 37%, with the highest proportion of the events in women. A retrospective study of 4240 patients taking malaria prophylaxis completed in 2009 also showed that mefloquine had the highest incidence of neuropsychiatric events among antimalarials, and that there were 22 deaths including 5 suicides associated with normal doses of the drug (Jacquerioz & Croft, 2009). There also have been clinical trials showing that mefloquine has a higher rate of discontinuation than either placebo (3.3% for mefloquine overall) or atovaquone and proguanil (5% vs. 3.9% of atovaquone and proguanil) due to GI upset, dizziness, and neuropsychological events (Kain et al., 2001; Hogh et al., 2000). Additionally, Mefloquine has been linked with an increased risk of seizures and cardiac arrhythmias, and a 2008 FDA post marketing review associated pneumonitis and eosinophilic pneumonia with the use of mefloquine (FDA, 2008).

Mefloquine is a safe choice for children and women. It is available in 250mg tablets, with the dose being 1 pill weekly for adults and for children over 45kg. Mefloquine should be taken with food or water. Prophylactic therapy should begin ≥ 2 weeks before travel to endemic areas, and must continue four weeks after leaving the area. The effectiveness of mefloquine against resistant species of plasmodium still makes it a good choice for travelers going to chloroquine resistant regions such as Africa, and the fact that it is safe in children and pregnant women make it a much more versatile drug. However, the neuropsychiatric adverse events and other side effects should be taken into account when choosing it as a prophylactic medication.

4.4 Doxycycline

Doxycycline is a broad-spectrum antibiotic derived from oxytetracycline that acts on the 30S ribosome subunit thus disrupting protein synthesis, and has activity against not only bacteria, but several parasitic diseases as well. It has a short half-life, necessitating daily

dosing and can be used as a malarial chemoprophylaxis in areas with known chloroquine and mefloquine resistance (Kain et al., 2001). It does not have activity against the exoerythorcytic stages of malaria making it a less efficacious choice for areas of the world with endemic *P. vivax* and *P. ovale.*

Several studies have shown the efficacy of prophylactic doxycycline in the prevention of malaria. In a double-blind, placebo controlled study doxycycline had 99% efficacy in the prevention of malaria in soldiers in Irian Jaya, Indonesia (Ohrt et al., 1997). In a separate trial investigating the prophylactic efficacy of azithromycin vs. doxycycline in 213 adult volunteers in a malaria endemic area it was found that daily doxycycline had an efficacy of 92.6% vs. 82.7% for daily azithromycin (Andersen et al., 1998). In addition, doxycycline was well tolerated in both of these studies.

While generally well tolerated, the most common side effects of doxycycline are primarily gastrointestinal including nausea, vomiting, diarrhea, glossitis, dysphagia, and rare instances of esophagitis and esophageal ulceration (Castelli et al., 2010). Doxycycline is a photosensitizing agent, and thus care must be taken to prevent over exposure to the sun while on this medication. Doxycycline also increases the risk for vaginal candidiasis by inhibiting the growth of natural vaginal flora. In a randomized, double-blind, placebo controlled trial of 623 non-immune travelers requiring short-term malaria chemoprophylaxis, doxycycline demonstrated a comparable side-effect profile to atovaquone/proquanal (Schlagenhauf et al., 2003). Importantly however, this study used doxycycline monohydrate, the more expensive form of the drug that has a favorable gastrointestinal side-effect profile. The findings of this study should not be extrapolated to the use of doxycycline hyclate or the non-enteric coated forms of doxycycline, where tolerability would likely be less favorable and might affect adherence to this chemoprophylactic drug.

The dosing for adults is 100mg daily. It is contraindicated in children under 8 years of age due to the risk of permanent discoloration of the teeth, and in pregnant or breast-feeding women due to the risk of toxicity to the fetus/infant (CDC, 2012). The recommended dosing for children ≥ 8 years of age is 2.2 mg/kg up to 100mg/day (CDC, 2012). Treatment should start one to two days before and last for 28 days after leaving an endemic area. Doxycycline should be taken with copious water to reduce the risk of esophagitis and may be taken with food to reduce GI side effects, although caution should be taken to avoid concomitant administration of antacids, magnesium salts, or bismuth subsalicylate as these may decrease intestinal absorption. The traveler should remain upright for at least 30 minutes following administration to reduce the risk of esophageal irritation or ulceration.

4.5 Atovaquone and proguanil hydrochloride

Atovaquone and proguanil is a combination antimalarial that works by inhibiting parasite mitochondrial electron transport and parasitic DNA synthesis by inhibiting dihydrofolate reductase. Proguanil significantly enhances the ability of atovaquone to inhibit parasitic mitochondrial electron transport (Kain et al., 2001; McKeage & Scott, 2003; Srivastava & Vaidya, 1999).

Atovaquone/proguanil is a once daily medication that is effective against both the erythrocytic and exoerythorcytic stages of malaria making this an acceptable choice not only for *P. falciprum,* but also *P. vivax and P. ovale,* both of which have hepatic life cycles. The efficacy of atovaquone as a causal prophylaxis was seen in a small volunteer challenge study

in which it was shown that parasites were eliminated prior to the establishment of erythrocytic infection, thus supporting causal efficacy (Shapiro et al., 1999). Atovaquone/proquanal has demonstrated efficacy for malaria prophylaxis in areas with predominantly *P. vivax* (Soto et al., 2006).

Atovaquone/proguanil's suppressive prophylaxis effectiveness has been shown in several clinical trials, three of which were among semi-immune populations in Gabon, Kenya, and Zambia and conducted as double-blinded, randomized, and placebo controlled trials, where overall efficacy of 98% in preventing malaria was observed in this population (Lell et al., 1998; Shanks et al., 1998; Sukwa et al., 1999; Kain et al., 2001). In two other large studies, in which non-immune travelers to malaria endemic regions were randomized to receive atovaquone/proguanil, mefloquine, or chloroquine plus proguanil, none of the patients in the atovaquone/proguanil arms who completed the study developed malaria (Hogh et al., 2000; Overbosch et al., 2001). It was also shown to be 100% effective against *P. falciparum* in non-immune Columbian soldiers (Soto et al., 2006). In a study of non-immune Indonesian immigrants, atovaquone/proguanil was 93% effective at preventing *P. falciparum* and 84% effective at preventing *P.vivax* (Ling et al., 2002).

The causal prophylactic activity of atovaquone/proguanil results in required dosing for only 1-week post exposure vs. up to 4 weeks with antimalarials that only have activity against the erythrocytic stage of the parasite, which may contribute to better adherence by travelers than some other malaria prophylaxis (Kain et al., 2001). In addition, the discontinuation rate due to side effects of the medication was found to be lower in atovaquone/proguanil then either mefloquine or chloroquine/proguanil (1.2%, vs. 5.0% and 0.2% vs. 2.0%, respectively) (Hogh et al., 2000; Overbosch et al., 2001). In a randomized control study, atovaquone/proguanil had a relatively low incidence of reported side effects compared to other available chemoprophylactic agents (Schlagenhauf et al., 2003). The most serious side effects of atovaquone/proguanil, although rare, include Steven-Johnson Syndrome, and a transient elevation of liver enzymes, while the most common were headache, abdominal pain, cough, diarrhea, and myalgias (McKeage & Scott, 2003).

Atovaquone/proguanil tablets are available in two formulations, adult and pediatric with the adult tablet containing 250mg of atovaquone and 100mg of proguanil, and the pediatric tablet containing 62.5 mg and 25mg of atovaquone and proguanil, respectively. Adult dosing is 1 adult tablet daily for 1-2 days before travel into an endemic area, daily throughout the stay, and then for 7 days once out of the endemic area. Dosing in the pediatric population is the same as for adults, except the number of pediatric tablets given daily is weight based. Atovaquone is highly a lipophilic compound in which the rate and extent of absorption is increased when taken with dietary fat, thus atovaquone/proguanil should be taken with food or a milky drink. While the safety of atovaquone/proguanil in the adult and pediatric populations has been shown through clinical trials, the safety during pregnancy is unknown and is contraindicated in this population. In addition, this medication should be avoided in mother's breastfeeding infants under 5kg and should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min).

While there are some case reports of resistance, in general atovaquone/proguanil is an efficacious, well-tolerated medication that should be considered first line in chloroquine and mefloquine resistant areas. The cost is higher than with other antimalarial chemoprophylactic drugs, which may limit its use in certain circumstances. Once atovaquone/proguanil becomes generic, this drug may be a more affordable option for malaria chemoprophylaxis in the future.

	Atovaquone /	Doxycycline	Primaquine	Mefloquine	Chloroquine
Adult Dose, scheduling	250mg/150mg once daily, 1-2 days before entering endemic region and 7 days after last exposure	100 mg once daily, 1-2 days before entering endemic region and 4 weeks after last exposure	30 mg base once daily, 1-2 days before entering endemic region and 7 days after last exposure	250 mg once weekly, 2 weeks before entering endemic region and 4 weeks after last exposure	500 mg (300mg base) once weekly, begin 1-2 weeks before entering endemic region and continue 4 weeks after last exposure
Pediatric	Yes for children 5 kg, weight based dose (only FDA-approved for children 11kg (see text)	Contraindicated < 8 years of age	Yes, weight based dose	Yes, for children >5kg and > 6 months, see text for children 5 kg or younger than 6 months of age	Yes, 5mg/kg base once weekly up to adult dose
Pregnancy	Insufficient data, not recommended	Contraindicated	Contraindicated	Yes	Yes
Limits on	None	4 months	None	None	None
Advantages	Very well tolerated, convenient, good efficacy	Inexpensive, relatively well tolerated, good efficacy, available worldwide	Inexpensive, relatively well tolerated, effective against all malaria species	Inexpensive, convenient, effective against all malaria species	Inexpensive, relatively well tolerated, convenient
Disadvantages	Expensive, contraindicated for poor renal function	Photosensitivity, increased risk for vaginal yeast infections, inconvenient	G6PD testing required before administration	Growing resistance, poorly tolerated, neurotoxicity, contraindicated with active or recent depression and other psychiatric disorders	Wide spread resistance, only useful in limited areas of the world
Comments	May become more affordable once generic.	May protect against rickettsial infections and leptospirosis as well as malaria	Not US FDA approved for chemoprophylaxis, dosing based on CDC recommendations	Contraindicated in those allergic to quinine/quinidine, cardiac conduction abnormalities	May worsen psoriasis

Table 1. Malaria Prophylaxis Options

5. Special populations

Children and pregnant women are at the highest risk for severe malaria when traveling to endemic areas and increased vigilance should be taken when dealing with these populations. It should be recommend that travel to endemic areas with a risk of transmission be avoided by these populations if possible, however if patients insist, the provider should stress that the traveler or the parents of the traveler insure that both personnel protective measures and chemoprophylaxis are strictly adhered to.

5.1 Pregnancy

Contracting malaria while pregnant puts the mother at an increased risk for adverse outcomes. Malaria infection during pregnancy has been associated with premature labor, abortion and stillbirth. The traveler should be counseled that the diagnosis of malaria in pregnancy may be difficult due to relatively low parasitemia at clinical presentation. A very high degree of suspicion should be taken when a pregnant women presents with fever in an endemic area, as missing the diagnosis could have grave consequences (McGready et al., 2004). Appropriate precautions should be followed including mosquito avoidance and control measures discussed previously as well as chemoprophylaxis when clinically indicated. Reviewing label-specific information and current CDC recommendations should be adhered to. There are no published data indicating elevated risks with the use of DEET in pregnant or lactating women, and current U.S. Environmental Protection Agency and CDC sources do not advise additional precautions for using FDA-approved insect repellants in this population (Koren et al., 2003; Zielinski-Gutierrez et al., 2012). Chemoprophylaxis in pregnancy is limited, as both doxycycline and primaquine are contraindicated, and atovoquone/proguanil is not currently recommended due to lack of safety data from clinical studies. Medications considered safe during pregnancy include chloroquine and mefloquine. While data in the past have only recommended mefloquine in the last half of pregnancy, current recommendations state that there is no evidence of adverse outcome if taken in any of the three trimesters of pregnancy when no other option is available (CDC, 2012).

5.2 Children

Children are at risk of malaria and the associated complications while traveling to endemic areas, and should have the same personal protective measures as adults. DEET has been shown to be safe and effective and is recommended for use by both the CDC and the American Academy of Pediatrics (AAP) for all children over 2 months of age at concentrations between 10-30% based on duration of protection required (Koren et al., 2003; AAP, 2009, 2011; CDC, 2012). Chemoprophylaxis for children is not as restricted as for pregnant women, with contraindications including doxycyline usage in children under 8 and primaquine usage in G6PD deficient patients. Atovaquone/proguanil is FDA approved for children greater than 11kg but recommended for off-label use by the CDC and AAP for children >5 kg. Mefloquine is only FDA approved for children > 5 kg and older than 6 months of age, but when necessary recommend off-label for children < 5kg and any age (AAP, 2009; CDC, 2012). Parents of very young infants should be counseled to avoid areas endemic for malaria given the risk of severe disease in this population. Adherence to personal protective measures and chemoprophylaxis if often poor in children, and thus it must be stressed to the traveling parent the importance of these precautions.

6. Existing challenges and future possibilities

As outlined in this chapter, there are only five available options for malaria chemoprophylaxis in the United States, one of which, primaquine, is not FDA approved for this indication. Emerging resistance, traveler intolerance, non-adherence, side effects and contraindications to existing options warrant development of newer agents for future chemoprophylactic use.

Resistance to existing drugs is well documented. Wide spread chloroquine resistance has led to the use of this drug in only very limited areas of the world, and mefloquine resistance continues to emerge. Doxycycline resistance has not been established and there is no well accepted definition or validated approach to measuring primaquine resistance (Baird, 2009). Primaquine tolerant or refractory strains of *P. vivax* have been well described, notably the Chesson strain from New Guinea (Collins & Jeffery, 1996). As resistance continues to emerge among existing options for the prevention of malaria, the importance of developing new and effective chemoprophylactic drugs for the international traveler becomes critical.

There are very few candidates currently being developed for malaria chemoprophylaxis, and the last FDA approval for this indication, atovoquone/proquanil, was over ten years ago in 2000. Doxycycline and mefloquine received FDA approval for malaria chemoprophylaxis in the preceding 11 years prior to the atovoquone/proquanil approval. The current lack of development of drugs for this indication is unprecedented and is cause for great concern.

Many reasons have been postulated for the lack of candidates in the developmental pipeline for the chemoprophylaxis indication. Obvious barriers are the lack of market incentive for this indication, although it is clear that the number of international non-immune travelers visiting endemic malarious regions has increased substantially in the last few decades, with case fatality rates ranging from 1-3% for falciparum malaria (Chen & Keystone, 2005). One challenge that has been attributed to stalled development in this area is the 5th Amendment to the Declaration of Helsinki (DH2000). First adopted by the World Medical Association (WMA) in 1964, the Declaration of Helsinki was an attempt to formally identify core ethical principles and guidelines for physicians and others involved in the design, execution and oversight of clinical research (Carlson et al., 2004). Principles relating to the use of placebo in clinical trials, post-trial access to investigational drugs, and social benefit as defined in DH2000, have presented challenges to existing models and development strategies for antimalarial chemoprophylactic drugs. Strategies to address these challenges in clinical development have been proposed (Dow et al., 2008).

Azithromycin, piperaquine, and tafenoquine have all been suggested as possible future chemoprophylactic drugs (Dow et al., 2008). Azithromycin has shown some promise, however future study is needed with combination agents to clarify its role for this indication (Chen & Keystone, 2005).

Tafenoquine, an 8-aminquinolone is a synthetic analogue of primaquine. First developed by the Walter Reed Army Institute of Research as WR238605 or etaquine, tafenoquine has a very long elimination half-life of approximately 14 days allowing weekly dosing. This novel compound shows promise for causal chemoprophylaxis against *P. falciparum* and *P. vivax*, as well as radical cure of *P. vivax.* It has been shown in rhesus monkeys to have 10x higher potency than primaquine for causal prophylaxis, and has demonstrated greater activity against blood and liver-stage parasites *in vitro.* (Cooper et al., 1994; Shanks et al., 2001).

In phase I studies of tafenoquine the drug is well tolerated with single doses up to 600mg and with chronic dosing (6 months) at 200mg weekly following a load of 200mg daily for 3 days (Brueckner et al., 1998; Leary et al., 2009) with no dose-limiting adverse events. The most common side effects observed are gastrointestinal, including heartburn, nausea and gas, usually associated with higher (>200mg) dosing. The most significant toxicity associated with tafenoquine is the potential to induce hemolysis in G6PD deficient individuals and methemoglobinemia (Crockett & Kain, 2007). GlaxoSmithKline, in partnership with Medicines for Malaria Venture, are undertaking an ascending-dose safety study of tafenoquine in G6PD heterozygous patients to identify the maximum safe dose in this population (MMV, 2011).

There have been several placebo-controlled trials evaluating tafenoquine as a causal antimalarial chemoprophylactic drug. In a study of non and semi-immune Thai soldiers, tafenoquine was administered monthly at 400mg, following a 1200mg loading dose (given as 400mg/day for 3 days) for a total of 6 months and demonstrated a protective efficacy 96% for *P. vivax* and 100% for multidrug-resistant *P. falciparum* (Walsh et al., 2004).

In a dose ranging prophylactic trial of tafenoquine to prevent *P. falciparum* in Gabon semi-immunes, which included children, doses of 25mg, 50mg, 100mg or 200mg/day for three consecutive days were tested. Tafenoquine was given one week following treatment with halofantrine. Subjects were actively followed for positive blood smears at day 56 and day 77 following tafenoquine dosing. Notwithstanding the 25mg dose, which uniformly failed, tafenoquine demonstrated 100% protective efficacy (PE) at all doses of 50mg or greater at day 56 and had PE of 80%, 93% and 100% at day 77 for doses of 50mg, 100mg and 200mg, respectively (Lell et al., 2000).

In a 13-week prophylactic trial in Kenyan semi-immune adults, tafenoquine was evaluated at weekly doses of 200mg and 400mg followed by a 600mg and 1200mg 3-day load, respectively. A third group consisted of a loading dose (1200mg load), followed by weekly placebo and a fourth group received placebo only throughout the 13-week period. The 200mg and 400mg weekly doses demonstrated PE of 91% and 93%, respectively. The loading dose only group had a PE of 80% (Shanks et al., 2001).

A large randomized, non-placebo controlled trial of non-immune Australian soldiers evaluated tafenoquine, dosed at 200mg weekly for 6 months following a loading dose (200mg/day for 3 days) while deployed to East Timor. Study participants were randomized 3:1 to receive either tafenoquine (n=492) or mefloquine (n=162) throughout their deployment. Although treatment-emergent adverse events were similar between the two groups and tafenoquine was well-tolerated during the study, there were no cases of malaria in any group. Exposure to malaria could not be assessed and therefore efficacy was not established (Nasveld et al., 2010).

In a subset of subjects (n=74) in the East Timor study who received tafenoquine, detailed safety assessments were conducted which detected vortex keratopathy. This finding had no effect on visual acuity and was fully resolved within one year following cessation of therapy (Nasveld et al., 2010). More extensive clinical ophthalmic evaluation of tafenoquine in a subsequent phase 1 safety trial further supports the vortex keratopathy seen with tafenoquine is not clinically significant (Leary et al., 2009).

Tafenoquine shows promise as a causal prophylactic drug and is currently being developed for a radical cure indication for *P. vivax* through a joint collaboration between GlaxoSmithKline and Medicines for Malaria Venture (MMV, 2011).

7. Conclusion

Addressing malaria chemoprophylaxis for the international traveler can be challenging and should be done within the context of a comprehensive medical evaluation well before visiting the endemic region. Malaria is a life-threatening illness and requires a multidimensional, individually tailored approach to ensure the most appropriate measures, including non-drug strategies, are taken to prevent infection if the traveler is exposed. Existing chemoprophylactic drugs offer effective options for the international traveler, however emerging resistance, side effect profiles and contraindications limit use in many circumstances. Future effort is needed to identify and develop new effective and safe options for malaria chemoprophylaxis.

The views expressed in this chapter are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Army or Air Force, the Department of Defense, nor the U.S. Government

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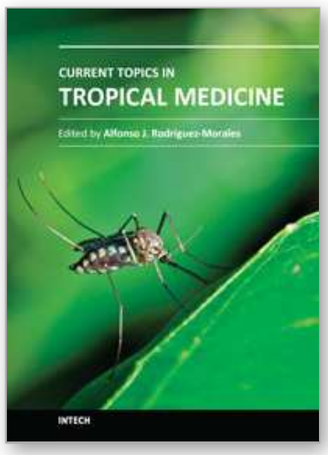

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