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Modern Malaria Chemoprophylaxis

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Contents

Abstract

Currently available medications for malaria chemoprophylaxis are efficacious but the problems of patient compliance, the advance of parasite drug resistance, and real or perceived serious adverse effects mean that new chemical compounds are needed.

Primaquine, which has been widely used to treat relapsing malaria since the 1950s, has been shown to prevent malaria when taken daily. Tafenoquine is a new 8-aminoquinoline with a much longer half-life than primaquine. Field trials to

date indicate that tafenoquine is efficacious and can be taken weekly or perhaps even less frequently. Both primaquine and tafenoquine require exact knowledge of a person's glucose 6-phosphate dehydrogenase status in order to prevent drug-induced haemolysis. Other potential malaria chemoprophylactic drugs such as third-generation antifol compounds and Mannich bases have reached advanced preclinical testing. Mefloquine has been seen to cause serious neuropsychiatric adverse effects on rare occasions. Recent public controversy regarding reputedly common serious adverse effects has made many Western travellers unwilling to take mefloquine.

Special risk groups exposed to malaria, such as long-term travellers, children, pregnant women, aircrew and those requiring unimpeded psychomotor reactions, migrants returning to visit malarious countries of origin and febrile persons who have returned from malaria endemic areas, all require a nuanced approach to the use of drugs to prevent malaria. The carrying of therapeutic courses of antimalarial drugs to be taken only if febrile illness develops is indicated in very few travellers despite its appeal to some who fear adverse effects more than they fear potentially lethal malaria infection. Travellers with a significant exposure to malaria require a comprehensive plan for prevention that includes anti-mosquito measures but which is still primarily be based on the regular use of efficacious antimalarial medications.

Malaria chemoprophylaxis is the prevention of malaria disease by giving healthy travellers medication prior to exposure to infective mosquitoes. Chemoprophylaxis is given to reduce the risk of malaria but is not perfectly effective, primarily because of noncompliance with medication regimens or parasite drug resistance. Prior to chloroquine resistance becoming widespread, decisions regarding malaria chemoprophylaxis were uncomplicated. Now that chloroquine alone is rarely indicated, multiple drugs and regimens are available to prevent malaria, each with its own advantages and problems. This review aims to present the current situation regarding malaria chemoprophylaxis, indicate what new drugs might be available in the future and discuss some of the common problems encountered when prescribing travellers chemoprophylaxis.

1. Molecular Basis for Drug Resistance to Past and Present Prophylactic Agents

The mechanism underlying the development of resistance to chemoprophylactic agents originates from chromosomal mutations in the malaria parasite. Until the late 1950s, chloroquine was the mainstay of malaria chemoprophylaxis, but widespread resistance now limits its usefulness in almost all malaria endemic countries. Compelling evidence exists that multiple mutations in the *Plasmodium falciparum* chloroquine resistance transporter gene (*pfcrt*) are associated with chloroquine resistance.[1,2] These mutations alter chloroquine concentrations in the food vacuole, a major digestive organelle of the malaria parasite that harbours protein transporters and is responsible for the degradation of host-derived haemoglobin. The food vacuole is a proven chemotherapeutic target for chloroquine.

Similar to chloroquine, the site of action for the arylamino-alcohols, such as mefloquine, is within

the digestive vesicle of the blood stage parasite where they complex with heme and prevent the detoxification of heme by crystallisation into the malaria pigment.[3] The mechanism of resistance to mefloquine is still unclear, but an increase in the copy number of the multidrug-resistance gene 1 (*pfmdr1*) may play an important role in modulating the sensitivity of the drug.[4]

Resistance to chloroquine took more than 20 years to eventuate, but resistance to the antifols, such as pyrimethamine and proguanil, and atovaquone, occurred shortly (<1 year) after their release. For antifols and sulfonamides, point mutations in the dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) genes, respectively, have been identified as causing structural alteration in the binding site of the target enzymes which diminishes the affinity of these enzymes for the antifolate drugs.[5-8] One to four mutations in DHFR confers a moderate to high level of resistance to DHFR inhibitors. The presence of mutations in DHFR appears to be more important in causing pyrimethamine/sulfadoxine failure than DHPS mutations.[9]

Similarly to DHFR inhibitors, resistance of *P. falciparum* to atovaquone occurs readily as a result of a high frequency of pre-existing mutations, with recrudescence occurring one-third of patients with falciparum malaria who are treated with atovaquone alone.[10] A single point mutation at codon 268 in the cytochrome *b* gene has been implicated in atovaquone resistance,[11,12] but other mutations may also be involved.[13] Although the synergistic action of atovaquone/proguanil differs from the folate pathway inhibition exhibited by pyrimethamine/sulfadoxine, the abundance of DHFR polymorphisms compromises the additional benefit from cycloguanil that arises with atovaquone/proguanil prophylaxis. It remains to be seen how quickly and to what extent resistance to atovaquone will appear once the drug is more widely used.

2. New Drugs for Malaria Chemoprophylaxis

Despite the increase in parasite drug resistance, new malaria chemoprophylactic drugs are introduced infrequently. The three currently available options in the US, mefloquine, doxycycline and atovaquone/proguanil, were approved for malaria prevention in 1989, 1992 and 2001, respectively. These regimens are presented in table I so that the reader can compare them with the different options that are discussed in this review. Chloroquine 300mg base weekly for an adult is an established chemoprophylaxis regimen, but it is not listed in the table as it is only appropriate in a very few places in the world, specifically Central America and Hispaniola.

More antimalarial drug development is undertaken now than has been previously, largely coordinated though the efforts of the Medicines for Malaria Venture (http://www.mmv.org). However, with one exception (tafenoquine), none of these new compounds are being developed primarily for malaria prevention. Generally, drugs found to effectively treat malaria infections are then adapted for the additional indication of chemoprophylaxis. The purpose of malaria chemoprophylaxis is to prevent potentially lethal malaria infections in travellers to malaria endemic areas.[14]

2.1 8-Aminoquinolines

Primaquine is the only currently approved compound of a group of chloroquine-related drugs known as the 8-aminoquinolines. This class of drugs has been extensively studied since World War II and a long-acting 8-aminoquinoline called tafenoquine is now in the advanced stages of clinical development for malaria chemoprophylaxis.

2.1.1 Primaquine for Prophylaxis

Primaquine is not a new drug, having been widely used to treat relapsing malaria since the 1950s.[15]

Table I. Antimalarial drugs for chemoprophylaxis, adult and paediatric regimens and adverse effects

Generic (trade) names	Dosage form	Adult regimen	Paediatric regimen	Common adverse events
Atovaquone/proguanil (Malarone®)	250mg of atovaquone and 100mg of proguanil (adult tablet) 62.5mg of atovaquone and 25mg of proguanil (paediatric tablet)	1 tablet/day	11–20kg: one-quarter adult tablet or one paediatric tablet 21–30kg: one-half adult tablet or two paediatric tablets 31–40kg: three-quarters adult tablet or three paediatric tablets >40kg: one adult tablet	Nausea, vomiting, abdominal pain, diarrhoea, increased transaminase levels, seizures, rash
Doxycycline (Vibramycin®, Vibra-Tabs®, Doryx®)	100mg tablet or capsule	100 mg/day	2.0 mg/kg/day (maximum 100 mg/day) <25kg or aged <8 years, contraindicated 25–35kg: 50mg 36–50kg: 75mg age >14 years: 100mg	Gastrointestinal upset, vaginal candidiasis, photosensitivity, allergic reactions, blood dyscrasias, azotaemia in renal diseases, hepatitis
Mefloquine (Lariam®, Mephaquin®)	250mg base tablet in EU (salt in the US)	250mg base/week (228mg base/week in the US)	<5kg: no data 5–15kg: 5 mg/kg once weekly 16–19kg: one-quarter tablet 20–30kg: one-half tablet 31–45kg: three-quarters tablet >45kg: one tablet once weekly	Dizziness, diarrhoea, nausea, vivid dreams, nightmares, irritability, mood alterations, headache, insomnia, anxiety, seizures, psychosis
Primaquine – terminal prophylaxis or radical cure	15mg base tablet	15mg base/day for 14 days	0.3mg base/kg/day for 14 days May require dosage increase to 0.6 mg/kg/day for primaquine-tolerant or resistant *Plasmodium vivax*	Gastrointestinal upset, haemolysis (in patients with glucose-6-phosphate dehydrogenase deficiency), methaemoglobinaemia

Unlike other current antimalarial drugs, primaquine primarily kills dormant stages of the parasite in the liver (hypnozoites), which then eliminates the risk of late malaria attacks long after leaving an endemic area (relapses). Primaquine can also kill the initial forms of the parasite that develop in the liver prior to invading the bloodstream. Killing all parasites in the liver prevents any blood infection and is known as causal prophylaxis. Causal prophylaxis is highly desirable as it limits the amount of medication that must be taken before and after leaving an endemic area, thus increasing patient compliance with chemoprophylaxis. On the basis of field trials primarily, but not exclusively, performed by the US Navy, a regimen of primaquine with a dosage increased beyond that used for treatment (30mg base vs 15mg daily in an adult) has been shown to causally prevent both falciparum and vivax malaria.[16-19]

The use of primaquine for malaria prophylaxis has recently been reviewed.[20] Although efficacious, malaria prophylaxis is not an approved indication for primaquine and this preventive therapy currently needs to be prescribed on a case by case basis, if a physician decides that primaquine is the best choice for an individual after informing the patient of the off-label nature of such usage. An absolute requirement prior to the use of primaquine for prophylaxis is the determination that the person has normal glucose-6-phosphate dehydrogenase (G6PD) enzyme activity in his/her erythrocytes. G6PD deficiency is a very common genetic polymorphism that can result in life-threatening haemolysis if such a person is given primaquine. Persons who might be considered for primaquine prophylaxis would include those who frequently have short-duration visits to highly malaria endemic areas. Such a person would require considerably fewer days on medication if he/she used primaquine compared with other daily medications for malaria prevention. If other forms of chemoprophylaxis are used during malaria exposure, primaquine given after leaving the endemic area is an established treatment course; this is known as terminal prophylaxis.[15] The current regimen used for primaquine treatment is shown in table I.

2.1.2 Tafenoquine

Tafenoquine, also known as WR 238605, is a new 8-aminoquinoline that is currently being co-developed by the Walter Reed Army Institute of Research and GlaxoSmithKline. It is a synthetic primaquine analogue that was initially developed in the search for a safer, more effective and longer-acting replacement for primaquine. In contrast with primaquine, tafenoquine possesses greater activity against blood and liver stages of malaria,[21,22] has greater sporontocidal activity[23] and is more active *in vitro* against multidrug-resistant asexual blood stages of *P. falciparum*.[24]

Tafenoquine has undergone single- and multiple-dose escalation studies, six phase II trials and a phase III study, and in excess of 2000 individuals have received the drug. In these studies, the drug has been well tolerated, with only mild and transient gastrointestinal disturbances and methaemoglobinaemia reported as adverse effects.[24-30] Other possible adverse effects include headache and mild, transient elevations in serum levels of liver-associated enzymes. In 1997, a randomised, placebo-controlled study showed that tafenoquine 200 or 400mg given weekly to adults provided protective efficacies of 86% and 89%, respectively, in an area holoendemic for *P. falciparum* in western Kenya.[26] As part of this trial, a 3-day treatment regimen of tafenoquine 400 mg/day followed by a weekly placebo protected 82% of participants for 7 weeks after commencement of drug administration. The prophylactic value of tafenoquine was further demonstrated in clinical studies in Ghana and Gabon, with protective efficacies of >86% using lower dose regimens of tafenoquine, such as 200mg weekly.[27,28]

The high protective efficacy of tafenoquine against *P. falciparum* malaria was further demon-

strated against *P. vivax* malaria in Thailand. A randomised, placebo-controlled study showed that, after a loading dose of tafenoquine 400 mg/day for 3 days followed by 6 months of single monthly doses of tafenoquine 400mg in Thai soldiers, the drug was 96% and 100% effective in preventing *P. vivax* and multidrug-resistant *P. falciparum* malaria, respectively.[25] Although tafenoquine is highly effective in suppressing the blood stages of both *P. falciparum* and *P. vivax*, it is no better than primaquine in preventing relapses of vivax malaria when used for post-exposure prophylaxis.[29] Furthermore, in Australian soldiers on peacekeeping duties in East Timor who received weekly tafenoquine 200mg for 6 months, vivax cases occurred during the 6-month follow-up period in a non-malarious area.[30]

Tafenoquine is a unique antimalarial drug. With its activity against all stages of the malaria parasite and its long elimination half-life, tafenoquine has the potential to be used for several indications. Tafenoquine is primarily being developed as a chemoprophylactic drug against both *P. falciparum* and *P. vivax* malaria, and for the radical treatment of vivax malaria in order to eradicate residual liver parasites. Tafenoquine may also find a role in post-exposure or terminal prophylaxis in travellers, in order to eliminate the hypnozoite stages of vivax malaria upon leaving an endemic area. If tafenoquine proves to be a practical malaria transmission-blocking drug, then there may be public health indications such as the use of tafenoquine during malaria epidemics, or in isolated areas with circumscribed transmission, such as islands in the Southwest Pacific region.

2.2 Third-Generation Antifols

In the 1940s, the first-generation antifols, pyrimethamine and cycloguanil (the active metabolite of proguanil), were developed as antimalarial drugs that targeted the parasite's DHFR enzyme. These DHFR inhibitors act by halting the synthesis of parasite DNA and protein subunits, thereby inhibiting parasite growth. However, the potency of the DHFR inhibitors has declined as a result of the emergence of drug-resistant parasite strains.[5-7]

Empirical drug screening by the Walter Reed Army Institute of Research led to the discovery in the mid 1960s of the second-generation antifol, WR 99210, which possessed marked activity against both pyrimethamine- and chloroquine-resistant isolates of *P. falciparum*.[31] Unfortunately, clinical trials of WR 99210 in volunteers showed that the drug induced severe gastrointestinal symptoms and had poor bioavailability and as a consequence, development of the drug was abandoned.[32] However, interest in WR 99210 has been maintained, particularly in its lack of cross-resistance with pyrimethamine and cycloguanil[31,33] and its use for the treatment of parasites containing multiple mutations in DHFR.[34]

On the basis of analogy, the biguanide precursor for WR 99210, PS 15 (also known as WR 250417) was designed and synthesised to circumvent the adverse events associated with WR 99210.[35] As a lipophilic biguanide, PS 15 was expected to be metabolically converted to WR 99210, but with improved bioavailability. PS 15 was found to be more active than either proguanil or WR 99210 in the treatment of multidrug-resistant *P. falciparum* in Aotus monkeys.[35] Further studies in monkeys demonstrated that PS 15 was converted to WR 99210,[36] and that PS 15 was better absorbed from the gastrointestinal tract than WR 99210.[37] Another feature of PS 15 is that it potentiates the *in vitro* activity of atovaquone and sulfamethoxazole.[35]

Although the prodrug PS 15 was a very attractive candidate for further development, the starting material, 2,4,5-trichlorophenol, had severe regulatory restrictions on its manufacture as the base material can be used to produce toxic substances such as dioxin.[38] The safety and regulatory restrictions associated with the manufacture of PS 15 provided the

impetus to develop analogues of PS 15, with antimalarial activity similar to or better than PS 15. Several of these third-generation antifols have now been developed, such as PS 26, JPC 2005 and JPC 2056, which maintain or exceed the *in vivo* antimalarial activity of PS 15.[38,39] Of these, JPC 2056 has been selected as the lead candidate, as it has equivalent efficacy to that of PS 15 and tolerability comparable with of proguanil.[39] Preclinical development of JPC 2056 is presently underway in a joint venture between Jacobus Pharmaceuticals Company and the Walter Reed Army Institute of Research.

2.3 Mannich Bases

The Mannich base, amodiaquine, has been the mainstay of this class of compound for the past 50 years. It is still used in Africa today, in areas of intense chloroquine resistance, for the treatment of uncomplicated falciparum malaria,[40,41] but is not recommended for prophylaxis as it can cause unacceptable adverse effects, including agranulocytosis and liver damage.[42,43] The formation of the electrophilic metabolite amodiaquine quinoneimine is believed to be responsible for the adverse effects of amodiaquine.[44] Isomeric amodiaquine analogues have been prepared that cannot form toxic quinoneimine metabolites via liver metabolism. On the basis of *in vitro* testing and *in vivo* activity in rodent malaria, isoquine has been shown to be more effective than amodiaquine.[44] Isoquine is easy to synthesise and is devoid of cross-resistance with either chloroquine or amodiaquine. It is currently in preclinical evaluation in a partnership between the Medicines for Malaria Venture and GlaxoSmith-Kline.[45]

Other Mannich base compounds have been synthesised for the treatment of malaria. New quinoline di-Mannich base compounds were found to be far more active than amodiaquine, chloroquine or pyronaridine in the *Saimiri*-bioassay model.[46] Briefly, in this test model the compounds are administered to non-infected *Saimiri sciureus* monkeys, and sera, containing both drug and metabolites, collected at various times after drug administration are incubated with *P. falciparum* parasites to assess for *in vitro* antimalarial activity. Several of these compounds were very active against multidrug-resistant *P. falciparum* isolates with no evidence of cross-resistance with chloroquine, mefloquine, halofantrine and atovaquone. The most potent of these compounds (TN 109) requires further evaluation to determine its value as a potential antimalarial drug.

In the 1970s, the Walter Reed Army Institute of Research also discovered the potential of Mannich bases for the treatment, and possibly the prevention, of malaria. Of these compounds, WR 228258 was the most potent. WR 228258 was about 140-fold more active than amodiaquine against the multidrug-resistant Smith strain of *P. falciparum*.[47] However, the drug was withdrawn as a result of toxicity concerns that appeared late in preclinical toxicological studies. Subsequently, a few more analogues have been synthesised and tested and, of these, WR 228979 was found to be the most promising, as it is chemically stable, with marked activity against multidrug-resistant *P. falciparum* strains *in vitro* and potency in mouse malaria models (DE Kyle, personal communication). Preclinical tolerance, pharmacological and treatment studies using the *P. falciparum*-Aotus model are now being planned for WR 228979 to see whether it will emerge as a new drug for the treatment and prevention of malaria infections.

3. Drugs that Should Not be Used for Chemoprophylaxis

Some antimalarial drugs that have well established therapeutic roles have no rational use as malaria chemoprophylactic agents. These drugs are listed in table II to avoid confusion should a physician need to use these drugs for malaria treatment or

Table II. Medications that should not be used for malaria chemoprophylaxis

Generic (trade) names	Severe adverse event or contraindication observed	References
Amodiaquine	Agranulocytosis and hepatitis	50,51
Halofantrine (Halfan™)	Cardiac dysrhythmias	52,53
Pyrimethamine/dapsone (Maloprim®)	Agranulocytosis	54
Pyrimethamine/sulfadoxine (Fansidar®)	Severe skin reactions (e.g. Stevens-Johnson syndrome)	55
Quinine	Long-term use predisposes to blackwater fever	56
Qinghaosu derivatives (i.e. artesunate)	Severe CNS lesions in animal studies argues against any long-term use of these short-acting treatment drugs	57

other indications. Although azithromycin has been tested for malaria chemoprophylaxis, it has insufficient efficacy against *P. falciparum* to recommend its use for malaria prevention.[48,49]

4. Public Controversy over Mefloquine

There is a growing public unease with the use of mefloquine for malaria chemoprophylaxis, the genesis of which is usually traced back to a BBC Watchdog television programme that appeared in the early 1990s. Although rare severe neuropsychiatric adverse effects are well described with mefloquine,[58] this controversy centred around the premise that mefloquine causes a great deal more serious psychiatric adverse effects than had been indicated by both the medical and pharmaceutical information available. The extent of the ongoing controversy, particularly via the Internet, makes it very difficult to untangle the various claims and counter-claims, especially since litigation is ongoing in several countries. This is important to the physician because of the increasing refusal and noncompliance rates associated with mefloquine prophylaxis. The recent safety and tolerability information on mefloquine is reviewed in sections 4.1 to 4.3 with a view to inform current prescribing practice.

4.1 Data on Mefloquine Tolerance

Mefloquine has a very important place in malaria chemoprophylaxis practice as the only weekly administered drug that is efficacious against chloroquine-resistant falciparum malaria. Historically, mefloquine was an essential addition to the armamentarium following the appearance of chloroquine-resistant *P. falciparum*. Mefloquine met a very important efficacy need and its use was shown to substantially decrease the frequency of malaria in US Peace Corps members in sub-Saharan Africa.[59] Although other efficacious options such as doxycycline were available, the practical effectiveness of daily regimens was often less than with weekly mefloquine because of compliance issues.[60] Several studies were carried out during the 1990s in response to growing public distrust of mefloquine. These consisted of both observational[61-66] and randomised clinical trials[67-70] where weekly mefloquine was compared with a variety of other daily medications. Despite the varied populations and study designs, the safety and tolerability of mefloquine for weekly malaria chemoprophylaxis was generally confirmed.

Some exceptions to this overall assessment were noted. Loading dose regimens that gave increased medication in the first week in order to more rapidly reach blood steady-state drug concentrations appeared to cause increased tolerability problems, particularly sleep disturbances.[67] The randomised, blinded, controlled trial that most closely resembled actual travel medicine practice in Europe and Canada showed no significant overall difference in tolerability between atovaquone/proguanil and mefloquine (71.4% vs 67.3% of patients, respectively [a difference of 4.1%; 95% CI −1.7, 9.9]).[70] However, travellers randomised to receive atovaquone/proguanil had a lower frequency of treatment-relat-

ed neuropsychiatric adverse effects, particularly those associated with sleep disturbances, than the mefloquine group (14% vs 29%; p = 0.001). Fewer adverse events of moderate or severe intensity and fewer treatment-related effects that caused prophylaxis to be discontinued were seen in persons receiving atovaquone/proguanil than in those randomised to receive mefloquine (0.2% vs 5.0%; p = 0.001).[70,71]

In a randomised, double-blind tolerability study with a placebo run-in phase that compared mefloquine, chloroquine/proguanil, doxycycline and atovaquone/proguanil in travellers attending travel clinics in Switzerland, Germany and Israel, withdrawals due to adverse effects were lowest in travellers who received atovaquone/proguanil (2%), followed by doxycycline (3%), mefloquine (4%) and chloroquine/proguanil (5%).[72] Of the four drugs tested, mefloquine was associated with the highest incidence of moderate-to-severe neuropsychiatric adverse effects and women reported significantly more neuropsychiatric, gastrointestinal and skin problems than men. Overall, atovaquone/proguanil and doxycycline were better tolerated than mefloquine and chloroquine/proguanil.

Neuropsychiatric diagnoses are very common in our modern society, and international travel itself is a stressful activity that makes assigning causality to any adverse effect noted in a previously healthy traveller extremely difficult. The most persuasive case for causality of mefloquine-induced adverse neuropsychiatric effects can be made when the previously undetected symptoms appear soon after starting the medication and resolve completely with its discontinuation. One large population-based study employed a UK-based General Practice Research Database involving >35 000 persons who were retrospectively examined for the first onset of depression, psychosis or panic attack following antimalarial drug use during the 1990s.[63] The incidence rates of depression during the use of mefloquine, doxycycline or proguanil and/or chloroquine, after being adjusted for age, gender and calendar year, were not markedly different at 6.9 (95% CI 4.5, 10.6), 9.5 (95% CI 3.7, 24.1) and 7.6 (95% CI 5.5, 10.5)/1000 person-years, respectively. The incidence rates of psychosis or panic attacks during mefloquine exposure were 1.0/1000 person-years (95% CI 0.3, 2.9) and 3.0/1000 person-years (95% CI 1.6, 5.7), respectively, approximately 2-fold higher than during use of doxycycline or proguanil and/or chloroquine, a difference which was not statistically significant.[63] If the question was reframed to look at all current users of mefloquine versus all previous users of other antimalarial drugs, then a significant increase in depression (odds ratio [OR] 8.0, 95% CI 1.0, 62.7; p < 0.05) and panic attacks (OR 2.7, 95% CI 1.1, 6.5; p < 0.05) was seen in the mefloquine group.[63]

4.2 Public Perceptions of Mefloquine Safety

In spite of the studies briefly summarised in section 4.1, and with no justifiable reason, many non-medical persons perceive mefloquine as a dangerous drug. The importance of this subpopulation is that many of them feel obligated to tell other travellers about rumoured or reported adverse experiences with mefloquine in an effort to stop its use. Since malaria chemoprophylaxis is by definition given to healthy persons in order to prevent a potentially lethal infectious disease,[73] these often outspokenly communicated negative views of mefloquine cause many persons to stop using mefloquine, thus negating the entire preventive effect. Given the number of studies already performed, it is unrealistic to expect that definitive data on either side of mefloquine prophylaxis safety issue will be found. A biologically plausible mechanism for severe adverse neuropsychiatric effects if mefloquine gains access to the CNS has been reported, further limiting any possibility of persuasive data to the contrary.[74] Post-marketing surveillance detected

sufficient adverse event concerns to cause the US FDA to require a specific patient information form to be given to all US recipients of mefloquine prescriptions.[75,76] Since the wording is similar to that of an informed consent agreement listing all potential adverse events, its negative effect on mefloquine acceptance is only too evident.

4.3 Failure of Prophylaxis as a Result of Not Taking Medication

One unambiguous outcome of the public controversy concerning neuropsychiatric adverse effects with mefloquine has been an increase in falciparum malaria in persons unwilling to take mefloquine. This has been seen in European travellers to Africa, where many tourists have been persuaded to accept malaria chemoprophylaxis advice from non-medical sources.[77-79] UK and US military populations deployed to West Africa have also experienced very high malaria attack rates when mefloquine was either not available because of logistical difficulties or was not taken as a result of concern about reported adverse effects.[80] If soldiers ordered to take mefloquine cannot be relied on to actually ingest the medication, who then should receive mefloquine prophylaxis? Given the unpredictable nature of compliance failure, mefloquine probably has only a small role, particularly for travellers who are living for an extended period in an area at very high risk for malaria. Mefloquine use is also limited by drug resistance, particularly in Southeast Asia.[81] However, travellers who have previously tolerated mefloquine well are good candidates to receive mefloquine on re-entering a malarious area as serious adverse effects following a previously tolerated course are either unknown or rare. The best indicator of whether mefloquine is a reasonable option for a traveller is his/her own attitude towards the medication. Any person expressing doubts or fears about a drug prior to travel will probably not comply with the medication sufficiently to be protected. In such a case, physicians can best serve the traveller by arranging an alternative regimen of chemoprophylaxis, even if it might be suboptimal based upon other considerations.

5. Special Risk Groups

There are special risk groups who do not easily adapt to any current chemoprophylaxis regimen. These travellers are often difficult to prescribe for because of either inadequate formulation availability, lack of safety data or high risk status. Although no certain rules can be applied to such travellers, it was felt important to discuss these individuals in order to explain the parameters that should be considered when faced with prescribing malaria chemoprophylaxis to these special risk groups.

5.1 Long-Term Travellers

It is a very unusual and compulsive person who will take antimalarial medications for a full year, yet some missionaries, aid workers and scientists go into malarious areas for a year or longer.[82] These persons are often some of the highest risk travellers in terms of contracting falciparum malaria in a setting where little or no professional medical support is available.[83] Prior to determining what form of malaria chemoprophylaxis may be appropriate, a careful history should be obtained concerning the geography of travel, anticipated time spent in the area, the housing in which the traveller will sleep and the availability of medical care, particularly the distance and time required to reach medical aid and its quality once accessed. The most up-to-date information on malaria risk areas and other useful traveller information can be found on governmental Internet sites such as those shown in table III.

Assessing a traveller's probable compliance is extremely important. Prescribing an elaborate form of chemoprophylaxis is probably useless in a person who expresses little desire or interest in taking regular medication, even after being informed of the

Table III. Selected websites with updated malaria risk and prevention information

Public health authority	URL
Public Health Agency of Canada	http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/04vol30/30s1/index.html
UK Health Protection Agency Advisory Committee on Malaria Prevention	http://www.hpa.org.uk/infections/topics_az/malaria/menu.htm
US Centers for Disease Control	http://www.cdc.gov/travel/regionalmalaria/index.htm
World Health Organization	http://whqlibdoc.who.int/publications/2005/9241580364_chap7.pdf

potentially lethal outcome of malaria.[84] Protection from mosquitoes and the use of screens and nets are of the utmost importance in preventing malaria in long-term travellers, particularly in providing a safe place to sleep. Instructions for their use are also often available on the websites listed in table III. Section 6 provides guidance on whether stand-by or presumptive therapy antimalarials would be advisable for an individual traveller.

Weekly mefloquine is usually recommended for long-term travellers in a highly malarious area.[85] Once a person knows that he/she tolerates mefloquine, it can be given confidently for extended periods of time and requires the least compliance effort from the traveller in order to maintain protective blood drug concentrations.[59,86,87] Some very compliant adults can consistently take doxycycline 100 mg/day and this can provide good protection over extended periods. However, doxycycline is not a good choice for anyone who cannot manage to take the medicine every day as it has a relatively rapid clearance (half-life of about 18 hours) from the blood. Daily atovaquone/proguanil is highly efficacious and very well tolerated, but it is generally too expensive to be realistically considered for most long-term travellers.[88] Sometimes a compromise can be reached, whereby a long-term traveller takes chemoprophylaxis when travelling from his/her usual residence in a low risk area to work temporarily in a much higher risk malarious area. The physician must balance chemoprophylactic efficacy against what the actual effectiveness of any regimen will be under the particular circumstances of a long-term traveller.

5.2 Infants and Children

Nearly all antimalarial drugs taste terrible and children object to taking them. Crushing tablets and placing them in food to disguise the taste does work but division of tablets is inexact, the role of the food in drug absorption is usually unknown and children are prone to spit out any undesired item, especially when the suspended drug still tastes foul. There are only two current choices for malaria chemoprophylaxis in small children: subdivided mefloquine tablets or the quarter-strength paediatric tablet of atovaquone/proguanil (see table I for current dosage regimens).[89-91] Some paediatricians recommend weekly mefloquine as it minimises the number of times a parent has to induce an unwilling child to take medication, thus increasing the effectiveness of the chemoprophylaxis. Atovaquone/proguanil prophylaxis has been widely used in the paediatric population and has shown an excellent safety and efficacy profile.[92] Doxycycline is contraindicated in young children because of the staining of teeth and bones. Chloroquine is worth mentioning, if only to warn parents about the risks to children. Despite the near universal presence of chloroquine resistance in malarious areas throughout the world, chloroquine is still very widely used. It is an all too common source of lethal poisonings in children who accidentally ingest only a few tablets and then die with intractable cardiac dysrrhythmias.[93] All medications should be kept out of the reach of children, but the ubiquity of chloroquine in some African settings makes it a risk about which it is particularly worth warning parents who are taking young children to the tropics.

There are no good guidelines for the use of antimalarial drugs in the very youngest infants (<5kg) because of a lack of relevant studies, although some public health authorities recommend the off-label use of mefloquine. This issue arises when immigrant parents wish to take babies back to the family's region of origin to be seen by other relatives. This is a distinctly risky proposition, especially in West Africa, and many physicians strongly encourage parents to delay such family visits to highly endemic areas until a child is older and better able to receive chemoprophylaxis. If parents insist on taking infants to highly endemic areas, then strict warnings about mosquito nets over the infant's bed and carrier is one recommended approach.

It is important to distinguish between the chemoprophylaxis of children travelling temporarily to a malarious area and intermittent presumptive therapy given to those indigenous children who grow up under the continuous threat of malaria infection. The latter case consists of repeated full-dose malaria treatment courses given as a public health tool to prevent severe malaria anaemia and to provide limited protection until natural immunity can develop.[94] Although potentially a very important strategy for the protection of infants in highly malarious areas, intermittent treatment with drugs, such as pyrimethamine/sulfadoxine, should not be considered as chemoprophylaxis and is not appropriate for the children of travellers.[95]

5.3 Pregnant Travellers

Malaria is potentially a very dangerous infection and this is particularly true for pregnant women and their fetuses. Indigenous women who have no choice in their malaria exposure pay an enormous price in ill-health and perinatal mortality associated with falciparum malaria.[96,97] A woman traveller with a choice of residence should avoid malarious areas during pregnancy. The best chemoprophylaxis can never protect a pregnant woman and her fetus as well as living in a non-endemic area. For those pregnant travellers who are unavoidably exposed to a risk of malaria, compulsive mosquito protection, particularly insecticide-treated bed nets and chemoprophylaxis, are strongly indicated.

The chemoprophylaxis options for pregnant women are not adequate. Weekly mefloquine has been studied in pregnant women and it does prevent malaria infection;[98] however, mefloquine treatment has been associated with increased rates of stillbirth[99] and prophylaxis has been associated with higher rates of spontaneous abortion.[100] Women are naturally reluctant to take a medication with even a small risk to the fetus and this must be balanced against an even greater risk should the mother develop acute falciparum malaria.

Doxycycline is contraindicated in women who are or who are trying to become pregnant because it stains developing teeth and bones. If a traveller taking doxycycline prophylaxis becomes pregnant, no action other than stopping the medication and, if necessary, switching to alternative protection is required. Fetal bones are not present, as such, during the first trimester and staining can be avoided by discontinuing the drug as soon as the pregnancy is discovered.

Atovaquone/proguanil has not been specifically examined for safety during pregnancy and is not approved for use in pregnant women. On the basis of what little is known about the two component drugs, the combination of atovaquone and proguanil is probably safe during pregnancy, but this has never been directly tested. The drug combination is listed as Pregnancy Category C, which is defined by the US FDA as "If animal reproduction studies have shown an adverse effect on the fetus, if there are no adequate and well-controlled studies in humans, and if the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks". Atovaquone/proguanil in combination with artesunate has been shown to be effective in the

treatment for multidrug-resistant falciparum malaria during pregnancy.[101,102] During this small study, no birth defects were seen, but there were suggestions that atovaquone was suboptimally absorbed in sick women. If one is faced with a pregnant woman who is unavoidably travelling to a highly malarious area, then atovaquone/proguanil is probably the single safest choice for chemoprophylaxis based on the inadequate knowledge available currently (table I).

5.4 Aircrew or Others Requiring Unimpeded Psychomotor Abilities

Aircrew are very difficult to prescribe malaria chemoprophylaxis for as it is practically impossible to prove that a drug does not cloud consciousness. Therefore, a much higher standard of evidence is required before medications are approved for aircrew than in the wider population.[103] There are some studies in pilots or pilot trainees that provide some guidance for chemoprophylaxis. Mefloquine has rare known severe adverse neuropsychiatric effects, which lead to aircrew being proscribed from receiving mefloquine.[104,105] This is despite studies in Swiss pilot trainees showing that it was generally as well tolerated as placebo.[66] A recent study examined both atovaquone/proguanil and primaquine in Canadian defence personnel in a placebo-controlled, double-blinded crossover design study.[106] Psychomotor testing and questionnaires showed no differences between those personnel given placebo, primaquine or atovaquone/proguanil. However, it is a good policy, whatever the selected chemoprophylaxis regimen, to have aircrew take the medication several days prior to flying to ascertain if there are any idiosyncratic reactions to the medication.

5.5 Migrants Returning to a Malarious Homeland

Migrants who return to their malarious homeland to visit friends and relatives are at much greater risk of contracting malaria than the general traveller to the same country.[107,108] Such migrants often visit rural areas where they are more exposed to infective mosquito bites. Returning migrants tend to have lax attitudes towards the danger of falciparum malaria, often due to the mistaken belief that a childhood in an endemic area provides adult immunity to malaria.[109,110] Resistance to malaria infection is obtained after many sequential infections and can quickly disappear when living in a non-malarious area.[111] As indicated in section 5.2, children of returning migrants who were born in non-malarious countries are at high risk of severe malaria if they do not receive chemoprophylaxis.[112] Problems associated with prevention of malaria in migrants returning to their country of origin include a lack of awareness of the risk of malaria and unwillingness or inability to pay for malaria chemoprophylaxis. Those found to have malaria on return are usually taking no chemoprophylaxis, as opposed to inappropriate medications. Since migrant communities often share social networks in their new home country, it is hoped that further efforts to inform migrant groups of their malaria risk when travelling will result in a greater proportion of these groups taking effective chemoprophylaxis.[113]

5.6 Febrile Returned Traveller Receiving Inadequate Chemoprophylaxis

Malaria in travellers often occurs after return to their nonmalarious home country. The delay from return to onset of illness can often be ≥2 months, particularly in the case of relapsing malaria, which has a dormant stage in the liver.[114] Although most febrile illnesses in returned travellers are not malaria, falciparum malaria it is the most serious infection and needs to be ruled out quickly.[115] Malaria blood films can be unhelpful if enough medication has been taken to suppress, but not prevent, falciparum malaria infection.[116] When taking a history from the febrile traveller it is critical to get an honest appraisal of the traveller's compliance with

chemoprophylaxis. A negative blood smear from a traveller who did not take any chemoprophylaxis is much more informative than one from a traveller who has been taking medication as directed and may have suppressed the parasites below detection. Mefloquine has a long half-life that can result in subacute presentation of suppressed falciparum malaria months after the end of malaria exposure, especially when the falciparum malaria is relatively resistant to mefloquine, as in parts of Southeast Asia.[86] Repeated blood smears and expert assistance when reading blood smears is often necessary, as the ability to read malaria smears well is an acquired skill that is vanishing as older medical technologists retire. Malaria antigen (generally histidine rich protein-2) detection cards can be useful, particularly when laboratory personnel are unaccustomed to examining blood smears for malaria parasites.[117]

Relapsing (*P. vivax* or *P. ovale*) malaria can occur several weeks or months after a traveller returns home.[115] This occurs even in persons who have complied perfectly with chemoprophylaxis, as none of the currently approved regimens eliminate the residual liver stage (hypnozoite). In some areas, especially the Southwest Pacific, vivax malaria predominates; such infections are relatively resistant to primaquine and can relapse repeatedly.[118] Even if a person has taken a standard regimen of primaquine (see table I), this does not exclude vivax malaria from the differential diagnosis of fever in a returned traveller.

Treatment of malaria in a febrile returned traveller who has apparently not responded to chemoprophylaxis is difficult since it is often not obvious whether malaria breakthrough has occurred as a result of patient noncompliance or drug resistance. If a returned traveller with falciparum malaria has been (supposedly) taking atovoquine/proguanil then a medication other than atovoquine/proguanil should be chosen for acute treatment, and this should usually be a rapidly acting drug such as quinine or an artemisinin derivative. Mefloquine prophylaxis failure can be treated with atovoquine/proguanil if the patient is not acutely ill, or quinine or an artemisinin derivative otherwise. Halofantrine is contraindicated in those who have recently received mefloquine. Doxycycline is cleared from the blood rapidly and, as such, does not prejudice the treatment of a patient who has not responded to chemoprophylaxis. Relapsing malaria such as *P. vivax* is the most common post-travel infection in those travellers who actually took their chemoprophylactic medication. *P. vivax* infection can usually be treated adequately with chloroquine followed by primaquine, but further relapses are a distinct possibility against which the patient needs to be counselled.[119,120]

6. Carrying Presumptive Therapy Instead of Chemoprophylaxis

When the emergence of chloroquine-resistant falciparum malaria left many travellers who were taking chloroquine with inadequate protection, some physicians evolved a strategy of having travellers to malaria endemic areas carry treatment courses of antimalarial drugs, with these patients not actually taking any medication unless they developed a febrile disease thought to be malaria.[121] This approach has appealed to many travellers as a form of 'trip insurance' against a presumably rare chance of a potentially lethal infection. As drug resistance has increased, selection of possible drug or drug combinations for such presumptive or stand-by therapy has become very limited. Use of presumptive stand-by therapy instead of malaria chemoprophylaxis is based on several assumptions and these need to be examined.

6.1 Problems of Presumptive Therapy

For low malaria risk areas, presumptive or stand-by therapy instead of chemoprophylaxis could be

justified by the uncertain quality of antimalarial drugs at the traveller's destination, the distance from reliable medical care and the speed of developing life-threatening complications from falciparum malaria in a non-immune traveller. Unfortunately, these points in favour of presumptive therapy are often interpreted by the traveller as meaning that seeking medical evaluation for febrile disease is unnecessary and that the traveller could proceed with their planned trip without risk after taking the medication. Travellers' resistance to seeking appropriate medical care locally, despite pre-travel advice to the contrary, seemed to confirm that many travellers viewed presumptive therapy as 'trip insurance' rather than a temporising medical intervention.[122]

Most febrile disease episodes, even in travellers to sub-Saharan Africa, are not caused by malaria, even if falciparum malaria is by far the most common potentially lethal infection.[123] One approach for trying to focus presumptive therapy on those most likely to have malaria was to include a blood diagnostic antigen-capture card along with the malaria medication after instructing the traveller on the use of the test and when to take the medication. This refinement is limited by the ability of sick travellers to perform the test and make medically sound decisions when sick and in unfamiliar settings.[124]

Given the practical limitations of presumptive or stand-by therapy, it is important to select such a strategy only for those most likely to benefit from it. There are exceptional travellers who work far from any medical care, such as some missionaries or field anthropologists, who truly need to be prepared to treat their own presumptive malaria attack before trekking out to find a physician. If these persons are in a very high malaria risk area, presumptive therapy needs to be coordinated with chemoprophylaxis and not used in its stead. This is particularly important when such long-term travellers are taking mefloquine, as subsequent presumptive treatment with halofantrine or quinine would be contraindicated because of the risk of fatal cardiac dysrrhymias.[125] Presumptive or stand-by therapy should only be chosen for very exceptional travellers, especially for those travelling to tropical Africa. If the risk of malaria is sufficient to be a serious concern for a particular traveller, then chemoprophylaxis is a better course of action than waiting for a potentially lethal infection when one has to rely on the traveller's own medical judgment and limited memory of what was discussed during pre-travel counselling.

6.2 Options for Presumptive Therapy

6.2.1 Atovaquone/Proguanil

If it is decided that a traveller needs to carry presumptive malaria therapy in addition to other malaria prevention measures, then atovaquone/proguanil is probably the first option to be considered.[126] This does not apply to those already taking atovaquone/proguanil prophylaxis. Its excellent safety and tolerability profile makes it a drug combination that can be given to travellers to very isolated areas with confidence that the medication itself is very unlikely to cause a severe adverse effect, even if taken incorrectly. It is dispensed in a single treatment course blister pack that can easily be carried to very remote locations. Atovaquone absorption is limited if the ill traveller is unable to eat, since fatty food enhances the bioavailability of the drug. Despite scattered reports of drug resistance, atovaquone/proguanil continues to have a very high cure rate for falciparum malaria.[13,127]

6.2.2 Artemisinin Combination Therapy

Artemisinin combination therapy (ACT) has become increasingly popular in Southeast Asia for malaria chemotherapy that delays the development of drug resistance, and ACT is also expected to be used more frequently in tropical Africa.[128] ACT can be a reasonable choice for an isolated traveller who needs presumptive therapy. However, two factors mitigate against the use of ACT in travellers,

particularly in Southeast Asia. Rarely is any traveller in Southeast Asia more than several hours from adequate medical care, and seeking a well informed local physician for treatment of a febrile illness is a much superior option to carrying stand-by medication. Also, fake or counterfeit antimalarial drugs are increasingly common, particularly in Southeast Asia but also in Africa.[129] Although it is possible to have a European traveller obtain ACT therapy of a known quality by being prescribed a registered combination of artemether/lumefantrine (CoArtem®)[1], this is not currently possible in the US or Canada.[130] Mefloquine is often the partner drug in ACT combination therapy in Southeast Asia and the adverse events associated with therapeutic doses of mefloquine are much greater than those seen with lower prophylactic doses of mefloquine.[131] Although ACT is an important chemotherapeutic strategy in the era of drug-resistant falciparum malaria, it should only be a very rare choice for a traveller as presumptive or stand-by therapy.

7. Conclusions

Preventive medications are used in order to protect a traveller during exposure to malaria. At least three separate processes are involved: the risk of malaria must be understood, the traveller must be willing to comply with a standard chemoprophylactic regimen, and the drug must be able to kill the parasite in the blood or liver of the traveller. Malaria prevention can be disrupted at any step in this chain of events. Finding an effective drug regimen that travellers will actually ingest is the practical challenge of the physician dealing with persons going to malaria endemic areas. There are hopeful indications that efficacious new drugs will soon be available to prevent malaria, despite the rapid advance of drug resistance. Better tolerated regimens that require less compliance from the traveller may be the key elements for improved malaria chemoprophylaxis in the future.

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References

1. Fidock DA, Nomura T, Talley AK, et al. Mutations in the *P. falciparum* digestive vacuole transmembrane protein PfCRT and evidence for their role in chloroquine resistance. Mol Cell 2000; 6 (4): 861-71
2. Ward SA, Bray PG. Definitive proof for a role of pfmdr 1 in quinoline resistance in *Plasmodium falciparum*. Drug Resist Updat 2000; 3 (2): 80-1
3. Bray PG, Janneh O, Raynes KJ, et al. Cellular uptake of chloroquine is dependent on binding to ferriprotoporphyrin IX and is independent of NHE activity in *Plasmodium falciparum*. J Cell Biol 1999; 145 (2): 363-76
4. Warhurst DC, Craig JC, Adagu IS. Lysosomes and drug resistance in malaria. Lancet 2002; 360 (9345): 1527-9
5. McCutchan TF, Welsh JA, Dame JB, et al. Mechanism of pyrimethamine resistance in recent isolates of *Plasmodium falciparum*. Antimicrob Agents Chemother 1984; 26 (5): 656-9
6. Cowman AF, Morry MJ, Biggs BA, et al. Amino acid changes linked to pyrimethamine resistance in the dihydrofolate reductase-thymidylate synthase gene of *Plasmodium falciparum*. Proc Natl Acad Sci U S A 1988; 85 (23): 9109-13
7. Peterson DS, Walliker D, Wellems TE. Evidence that a point mutation in dihydrofolate reductase-thymidylate synthase confers resistance to pyrimethamine in falciparum malaria. Proc Natl Acad Sci U S A 1988; 85 (23): 9114-8
8. Triglia T, Menting JG, Wilson C, et al. Mutations in dihydropteroate synthase are responsible for sulfone and sulfonam-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

ide resistance in *Plasmodium falciparum*. Proc Natl Acad Sci U S A 1997; 94 (25): 13944-9
9. Basco LK, Tahar R, Ringwald P. Molecular basis of in vivo resistance to sulfadoxine-pyrimethamine in African adult patients infected with *Plasmodium falciparum* malaria parasites. Antimicrob Agents Chemother 1998; 42 (7): 1811-4
10. Looareesuwan S, Viravan C, Webster HK, et al. Clinical studies of atovaquone, alone or in combination with other antimalarial drugs, for treatment of acute uncomplicated malaria in Thailand. Am J Trop Med Hyg 1996; 54 (1): 62-6
11. Schwartz E, Bujanover S, Kain KC. Genetic confirmation of atovaquone-proguanil-resistant *Plasmodium falciparum* malaria acquired by a nonimmune traveler to East Africa. Clin Infect Dis 2003; 37 (3): 450-1
12. Korsinczky M, Chen N, Kotecka B, et al. Mutations in *plasmodium falciparum* cytochrome b that are associated with atovaquone resistance are located at a putative drug-binding site. Antimicrob Agents Chemother 2000; 44 (8): 2100-8
13. Wichmann O, Muehlen M, Gruss H, et al. Malarone treatment failure not associated with previously described mutations in the cytochrome b gene. Malar J 2004; 3 (1): 14
14. Newman RD, Parise ME, Barber AM, et al. Malaria-related deaths among US travelers, 1963-2001. Ann Intern Med 2004; 141 (7): 547-55
15. Baird JK, Hoffman SL. Primaquine therapy for malaria. Clin Infect Dis 2004; 39 (9): 1336-45
16. Baird JK, Lacy MD, Basri H, et al. Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. Clin Infect Dis 2001; 33 (12): 1990-7
17. Schwartz E, Regev-Yochay G. Primaquine as prophylaxis for malaria for nonimmune travelers: a comparison with mefloquine and doxycycline. Clin Infect Dis 1999; 29 (6): 1502-6
18. Fryauff DJ, Baird JK, Purnomo, et al. Malaria in a nonimmune population after extended chloroquine or primaquine prophylaxis. Am J Trop Med Hyg 1997; 56 (2): 137-40
19. Baird JK, Fryauff DJ, Basri H, et al. Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. Am J Trop Med Hyg 1995; 52 (6): 479-84
20. Baird JK, Fryauff DJ, Hoffman SL. Primaquine for prevention of malaria in travelers. Clin Infect Dis 2003; 37 (12): 1659-67
21. Peters W, Robinson BL, Milhous WK. The chemotherapy of rodent malaria. LI: studies on a new 8-aminoquinoline, WR 238,605. Ann Trop Med Parasitol 1993; 87 (6): 547-52
22. Puri SK, Dutta GP. Blood schizontocidal activity of WR 238605 (Tafenoquine) against *Plasmodium cynomolgi* and *Plasmodium fragile* infections in rhesus monkeys. Acta Trop 2003; 86 (1): 35-40
23. Ponsa N, Sattabongkot J, Kittayapong P, et al. Transmission-blocking activity of tafenoquine (WR-238605) and artelinic acid against naturally circulating strains of *Plasmodium vivax* in Thailand. Am J Trop Med Hyg 2003; 69 (5): 542-7
24. Brueckner RP, Lasseter KC, Lin ET, et al. First-time-in-humans safety and pharmacokinetics of WR 238605, a new antimalarial. Am J Trop Med Hyg 1998; 58 (5): 645-9
25. Walsh DS, Eamsila C, Sasiprapha T, et al. Efficacy of monthly tafenoquine for prophylaxis of *Plasmodium vivax* and multidrug-resistant *P. falciparum* malaria. J Infect Dis 2004; 190 (8): 1456-63
26. Shanks GD, Oloo AJ, Aleman GM, et al. A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against *Plasmodium falciparum* malaria. Clin Infect Dis 2001; 33 (12): 1968-74
27. Hale BR, Owusu-Agyei S, Fryauff DJ, et al. A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against *Plasmodium falciparum*. Clin Infect Dis 2003; 36 (5): 541-9
28. Lell B, Faucher JF, Missinou MA, et al. Malaria chemoprophylaxis with tafenoquine: a randomised study. Lancet 2000; 355 (9220): 2041-5
29. Nasveld P, Kitchener S, Edstein M, et al. Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. Trans R Soc Trop Med Hyg 2002; 96 (6): 683-4
30. Nasveld P, Brennan L, Edstein M. A randomised, double-blind comparative study to evaluate the safety, tolerability and effectiveness of tafenoquine and mefloquine for the prophylaxis of malaria in non-immune Australian soldiers [abstract no. 326]. Am J Trop Med Hyg 2002; 67 (2): 255
31. Rieckmann K. The in vitro activity of experimental antimalarial compounds against strains of *Plasmodium falciparum* with varying degrees of sensitivity to pyrimethamine and chloroquine. In: Chemotherapy of malaria and resistance to antimalarials. WHO Technical Report Series, No. 529. Geneva: World Health Organization, 1973: 58
32. Canfield C. New antimalarials under development. In: Bruce-Chwatt L, editor. Chemotherapy of malaria. Rev. 2nd ed. Monograph series 27. Geneva: World Health Organization, 1986: 99-100
33. Childs GE, Lambros C. Analogues of N-benzyloxydihydrotriazines: in vitro antimalarial activity against *Plasmodium falciparum*. Ann Trop Med Parasitol 1986; 80 (2): 177-81
34. Fidock DA, Nomura T, Wellems TE. Cycloguanil and its parent compound proguanil demonstrate distinct activities against *Plasmodium falciparum* malaria parasites transformed with human dihydrofolate reductase. Mol Pharmacol 1998; 54 (6): 1140-7
35. Canfield CJ, Milhous WK, Ager AL, et al. PS-15: a potent, orally active antimalarial from a new class of folic acid antagonists. Am J Trop Med Hyg 1993; 49 (1): 121-6
36. Edstein MD, Corcoran KD, Shanks GD, et al. Evaluation of WR250417 (a proguanil analog) for causal prophylactic activity in the *Plasmodium cynomolgi-Macaca mulatta* model. Am J Trop Med Hyg 1994; 50 (2): 181-6
37. Rieckmann KH, Yeo AE, Edstein MD. Activity of PS-15 and its metabolite, WR99210, against *Plasmodium falciparum* in an in vivo-in vitro model. Trans R Soc Trop Med Hyg 1996; 90 (5): 568-71
38. Jensen NP, Ager AL, Bliss RA, et al. Phenoxypropoxybiguanides, prodrugs of DHFR-inhibiting diaminotriazine antimalarials. J Med Chem 2001; 44 (23): 3925-31
39. Schiehser G, Shieh H-M, Nevchas I. Selection of the third generation antifolate, JPC-2056, as a pre-clinical development candidate [abstract no. 727]. Am J Trop Med Hyg 2004; 71 (4): 215

40. Rwagacondo CE, Niyitegeka F, Sarushi J, et al. Efficacy of amodiaquine alone and combined with sulfadoxine-pyrimethamine and of sulfadoxine pyrimethamine combined with artesunate. Am J Trop Med Hyg 2003; 68 (6): 743-7
41. Abacassamo F, Enosse S, Aponte JJ, et al. Efficacy of chloroquine, amodiaquine, sulphadoxine-pyrimethamine and combination therapy with artesunate in Mozambican children with non-complicated malaria. Trop Med Int Health 2004; 9 (2): 200-8
42. Hatton CS, Peto TE, Bunch C, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. Lancet 1986; I (8478): 411-4
43. Neftel KA, Woodtly W, Schmid M, et al. Amodiaquine induced agranulocytosis and liver damage. BMJ (Clin Res Ed) 1986; 292 (6522): 721-3
44. O'Neill PM, Mukhtar A, Stocks PA, et al. Isoquine and related amodiaquine analogues: a new generation of improved 4-aminoquinoline antimalarials. J Med Chem 2003; 46 (23): 4933-45
45. Fidock DA, Rosenthal PJ, Croft SL, et al. Antimalarial drug discovery: efficacy models for compound screening. Nat Rev Drug Discov 2004; 3 (6): 509-20
46. Kotecka BM, Barlin GB, Edstein MD, et al. New quinoline di-Mannich base compounds with greater antimalarial activity than chloroquine, amodiaquine, or pyronaridine. Antimicrob Agents Chemother 1997; 41 (6): 1369-74
47. Sweeney T, Pick R. 4-Aminoquinolines and Mannich Bases. New York: Springer-Verlag, 1984
48. Andersen SL, Oloo AJ, Gordon DM, et al. Successful double-blinded, randomized, placebo-controlled field trial of azithromycin and doxycycline as prophylaxis for malaria in western Kenya. Clin Infect Dis 1998; 26 (1): 146-50
49. Anderson SL, Berman J, Kuschner R, et al. Prophylaxis of *Plasmodium falciparum* malaria with azithromycin administered to volunteers. Ann Intern Med 1995; 123 (10): 771-3
50. Rouveix B, Coulombel L, Aymard JP, et al. Amodiaquine-induced immune agranulocytosis. Br J Haematol 1989; 71 (1): 7-11
51. Larrey D, Castot A, Pessayre D, et al. Amodiaquine-induced hepatitis: a report of seven cases. Ann Intern Med 1986; 104 (6): 801-3
52. Sowunmi A, Falade CO, Oduola AM, et al. Cardiac effects of halofantrine in children suffering from acute uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg 1998; 92 (4): 446-8
53. Sudden death in a traveller following halofantrine administration: Togo, 2000. Can Commun Dis Rep 2001; 27 (14): 120-1, 124
54. Hutchinson DB, Whiteman PD, Farquhar JA. Agranulocytosis associated with maloprim: review of cases. Hum Toxicol 1986; 5 (4): 221-7
55. Miller KD, Lobel HO, Satriale RF, et al. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. Am J Trop Med Hyg 1986; 35 (3): 451-8
56. Bruce-Chwatt LJ. Quinine and the mystery of blackwater fever. Acta Leiden 1987; 55: 181-96
57. Genovese RF, Newman DB, Brewer TG. Behavioral and neural toxicity of the artemisinin antimalarial, arteether, but not artesunate and artelinate, in rats. Pharmacol Biochem Behav 2000; 67 (1): 37-44
58. Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992-1998: a review. J Travel Med 1999; 6 (2): 122-33
59. Lobel HO, Miani M, Eng T, et al. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993; 341 (8849): 848-51
60. Sanchez JL, DeFraites RF, Sharp TW, et al. Mefloquine or doxycycline prophylaxis in US troops in Somalia. Lancet 1993; 341 (8851): 1021-2
61. Barrett PJ, Emmins PD, Clarke PD, et al. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. BMJ 1996; 313 (7056): 525-8
62. Jaspers CA, Hopperus Buma AP, van Thiel PP, et al. Tolerance of mefloquine chemoprophylaxis in Dutch military personnel. Am J Trop Med Hyg 1996; 55 (2): 230-4
63. Meier CR, Wilcock K, Jick SS. The risk of severe depression, psychosis or panic attacks with prophylactic antimalarials. Drug Saf 2004; 27 (3): 203-13
64. Peragallo MS, Sabatinelli G, Sarnicola G. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). Trans R Soc Trop Med Hyg 1999; 93 (1): 73-7
65. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. Lancet 1993; 341 (8856): 1299-303
66. Schlagenhauf P, Lobel H, Steffen R, et al. Tolerance of mefloquine by SwissAir trainee pilots. Am J Trop Med Hyg 1997; 56 (2): 235-40
67. Boudreau E, Schuster B, Sanchez J, et al. Tolerability of prophylactic Lariam regimens. Trop Med Parasitol 1993; 44 (3): 257-65
68. Croft AM, Clayton TC, World MJ. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. Trans R Soc Trop Med Hyg 1997; 91 (2): 199-203
69. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997; 126 (12): 963-72
70. Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001; 33 (7): 1015-21
71. van Riemsdijk MM, Sturkenboom MC, Ditters JM, et al. Atovaquone plus chloroguanide versus mefloquine for malaria prophylaxis: a focus on neuropsychiatric adverse events. Clin Pharmacol Ther 2002; 72 (3): 294-301
72. Schlagenhauf P, Tschopp A, Johnson R, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: multicentre, randomised, double blind, four arm study. BMJ 2003; 327 (7423): 1078
73. Kain KC, MacPherson DW, Kelton T, et al. Malaria deaths in visitors to Canada and in Canadian travellers: a case series. CMAJ 2001; 164 (5): 654-9

74. Weiss SM, Benwell K, Cliffe IA, et al. Discovery of nonxanthine adenosine A2A receptor antagonists for the treatment of Parkinson's disease. Neurology 2003; 61 (11 Suppl. 6): S101-6
75. FDA requires warnings on anti-malaria drug Lariam. Consum Rep 2004; 69 (1): 45
76. Medication guide: Lariam® [online]. Available from URL: http://www.fda.gov/medwatch/SAFETY/2003/LariamMedGuide.pdf [Accessed 2005 Jun 29]
77. Farquharson L, Noble LM, Barker C, et al. Health beliefs and communication in the travel clinic consultation as predictors of adherence to malaria chemoprophylaxis. Br J Health Psychol 2004; 9 (Pt 2): 201-17
78. Reid AJ, Whitty CJ, Ayles HM, et al. Malaria at Christmas: risks of prophylaxis versus risks of malaria. BMJ 1998; 317 (7171): 1506-8
79. Muehlberger N, Jelinek T, Schlipkoeter U, et al. Effectiveness of chemoprophylaxis and other determinants of malaria in travellers to Kenya. Trop Med Int Health 1998; 3 (5): 357-63
80. Lessells R, Jones ME, Welsby PD. A malaria outbreak following a British military deployment to Sierra Leone. J Infect 2004; 48 (2): 209-10
81. Wongsrichanalai C, Pickard AL, Wernsdorfer WH, et al. Epidemiology of drug-resistant malaria. Lancet Infect Dis 2002; 2 (4): 209-18
82. Hughes C, Tucker R, Bannister B, et al. Malaria prophylaxis for long-term travellers. Commun Dis Public Health 2003; 6 (3): 200-8
83. Blanke CH. Increased malaria-morbidity of long-term travellers due to inappropriate chemoprophylaxis recommendations. Trop Doct 2003; 33 (2): 117-9
84. Malaria deaths following inappropriate malaria chemoprophylaxis: United States, 2001. MMWR Morb Mortal Wkly Rep 2001; 50 (28): 597-9
85. Knobloch JU. Long-term malaria prophylaxis for travelers. J Travel Med 2004; 11 (6): 374-8
86. Hopperus Buma AP, van Thiel PP, Lobel HO, et al. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. J Infect Dis 1996; 173 (6): 1506-9
87. Lobel HO, Varma JK, Miani M, et al. Monitoring for mefloquine-resistant *Plasmodium falciparum* in Africa: implications for travelers' health. Am J Trop Med Hyg 1998; 59 (1): 129-32
88. Overbosch D. Post-marketing surveillance: adverse events during long-term use of atovaquone/proguanil for travelers to malaria-endemic countries. J Travel Med 2003; 10 Suppl. 1: S16-20
89. Stauffer WM, Kamat D, Magill AJ. Traveling with infants and children. Part IV: insect avoidance and malaria prevention. J Travel Med 2003; 10 (4): 225-40
90. Fischer PR, Bialek R. Prevention of malaria in children. Clin Infect Dis 2002; 34 (4): 493-8
91. Kramer MH, Lobel HO. Antimalarial chemoprophylaxis in infants and children. Paediatr Drugs 2001; 3 (2): 113-21
92. Camus D, Djossou F, Schilthuis HJ, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. Clin Infect Dis 2004; 38 (12): 1716-23
93. Collee GG, Samra GS, Hanson GC. Chloroquine poisoning: ventricular fibrillation following 'trivial' overdose in a child. Intensive Care Med 1992; 18 (3): 170-1
94. Geerligs PD, Brabin BJ, Eggelte TA. Analysis of the effects of malaria chemoprophylaxis in children on haematological responses, morbidity and mortality. Bull World Health Organ 2003; 81 (3): 205-16
95. Alonzo Gonzalez M, Menendez C, Font F, et al. Cost-effectiveness of iron supplementation and malaria chemoprophylaxis in the prevention of anaemia and malaria among Tanzanian infants. Bull World Health Organ 2000; 78 (1): 97-107
96. van Geertruyden JP, Thomas F, Erhart A, et al. The contribution of malaria in pregnancy to perinatal mortality. Am J Trop Med Hyg 2004; 71 (2 Suppl.): 35-40
97. Guyatt HL, Snow RW. Impact of malaria during pregnancy on low birth weight in sub-Saharan Africa. Clin Microbiol Rev 2004; 17 (4): 760-9
98. Nosten F, ter Kuile F, Maelankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. J Infect Dis 1994; 169 (3): 595-603
99. Nosten F, Vincenti M, Simpson J, et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999; 28 (4): 808-15
100. Smoak BL, Writer JV, Keep LW, et al. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis 1997; 176 (3): 831-3
101. McGready R, Keo NK, Villegas L, et al. Artesunate-atovaquone-proguanil rescue treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy: a preliminary report. Trans R Soc Trop Med Hyg 2003; 97 (5): 592-4
102. McGready R, Stepniewska K, Edstein MD, et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol 2003; 59 (7): 545-52
103. Byrne NJ, Behrens RH. Airline crews' risk for malaria on layovers in urban sub-saharan Africa: risk assessment and appropriate prevention policy. J Travel Med 2004; 11 (6): 359-61
104. Chambers JA. Military aviators, special operations forces, and causal malaria prophylaxis. Mil Med 2003; 168 (12): 1001-6
105. Barron BA. Chemoprophylaxis in US Naval aircrew transiting malaria endemic areas. Aviat Space Environ Med 1998; 69 (7): 656-65
106. Paul MA, McCarthy AE, Gibson N, et al. The impact of Malarone and primaquine on psychomotor performance. Aviat Space Environ Med 2003; 74 (7): 738-45
107. Leder K, Black J, O'Brien D, et al. Malaria in travelers: a review of the GeoSentinel surveillance network. Clin Infect Dis 2004; 39 (8): 1104-12
108. Loutan L. Malaria: still a threat to travellers. Int J Antimicrob Agents 2003; 21 (2): 158-63
109. Schlagenhauf P, Steffen R, Loutan L. Migrants as a major risk group for imported malaria in European countries. J Travel Med 2003; 10 (2): 106-7
110. Castelli F, Matteelli A, Caligaris S, et al. Malaria in migrants. Parassitologia 1999; 41 (1-3): 261-5

111. Lalloo DG, Trevett AJ, Paul M, et al. Severe and complicated falciparum malaria in Melanesian adults in Papua New Guinea. Am J Trop Med Hyg 1996; 55 (2): 119-24

112. Ladhani S, El Bashir H, Patel VS, et al. Childhood malaria in East London. Pediatr Infect Dis J 2003; 22 (9): 814-9

113. Cleary VA, Figueroa JI, Heathcock R, et al. Improving malaria surveillance in inner city London: is there a need for targeted intervention? Commun Dis Public Health 2003; 6 (4): 300-4

114. Schwartz E, Parise M, Kozarsky P, et al. Delayed onset of malaria: implications for chemoprophylaxis in travelers. N Engl J Med 2003; 349 (16): 1510-6

115. D'Acremont V, Landry P, Mueller I, et al. Clinical and laboratory predictors of imported malaria in an outpatient setting: an aid to medical decision making in returning travelers with fever. Am J Trop Med Hyg 2002; 66 (5): 481-6

116. Klement E, Chauveheid MP, Thellier M, et al. Subacute clinical forms of *Plasmodium falciparum* malaria in travelers receiving chloroquine-proguanil prophylaxis. Clin Infect Dis. 2001 Jul 1; 33 (1): e1-2. Epub 2001 May 23

117. Wongsrichanalai C, Gasser Jr RA. Current status of malaria rapid diagnostic devices: an update. Trends Parasitol 2002; 18 (3): 107-8

118. Baird JK, Rieckmann KH. Can primaquine therapy for vivax malaria be improved? Trends Parasitol 2003; 19 (3): 115-20

119. Centers for Disease Control and Prevention. Guidelines for treatment of malaria in the United States (based on drugs currently available for use in the United States) [online]. Available from URL: http://www.cdc.gov/malaria/pdf/treatmenttable.pdf [Accessed 2005 Jul 26]

120. Suh KN, Kain KC, Keystone JS. Malaria. CMAJ 2004 May 25; 170 (11): 1693-702

121. Schlagenhauf P, Steffen R. Stand-by treatment of malaria in travellers: a review. J Trop Med Hyg 1994; 97 (3): 151-60

122. Schlagenhauf P, Steffen R, Tschopp A, et al. Behavioural aspects of travellers in their use of malaria presumptive treatment. Bull World Health Organ 1995; 73 (2): 215-21

123. Nothdurft HD, Jelinek T, Pechel SM, et al. Stand-by treatment of suspected malaria in travellers. Trop Med Parasitol 1995; 46 (3): 161-3

124. Whitty CJM, Armstrong M, Behrens RH. Self-testing for falciparum malaria with antigen-capture cards by travelers with symptoms of malaria. Am J Trop Med Hyg 2000; 63 (5-6): 295-7

125. Touze JE, Fourcade L, Peyron F, et al. Is halofantrine still advisable in malaria attacks? Ann Trop Med Parasitol 1997; 91 (7): 867-73

126. McKeage K, Scott L. Atovaquone/proguanil: a review of its use for the prophylaxis of *Plasmodium falciparum* malaria. Drugs 2003; 63 (6): 597-623

127. Giao PT, De Vries PJ, Hung LQ, et al. Atovaquone-proguanil for recrudescent *Plasmodium falciparum* in Vietnam. Ann Trop Med Parasitol 2003; 97 (6): 575-80

128. White NJ. Antimalarial drug resistance. J Clin Invest 2004; 113 (8): 1084-92

129. Newton P, Proux S, Green M, et al. Fake artesunate in southeast Asia. Lancet 2001; 357 (9272): 1948-50

130. Wernsdorfer WH. Coartemether (artemether and lumefantrine): an oral antimalarial drug. Expert Rev Anti Infect Ther 2004; 2 (2): 181-96

131. Rendi-Wagner P, Noedl H, Wernsdorfer WH, et al. Unexpected frequency, duration and spectrum of adverse events after therapeutic dose of mefloquine in healthy adults. Acta Trop 2002; 81 (2): 167-73

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