Malaria prophylaxis: make the right choice for travellers with special circumstances

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Case scenario

Mr Brown is going to work on a construction site in northern Mozambique, along the coastline, for a year. Mrs Brown and Jimmy, her 16-year-old son, and Julie, her four-year-old daughter, will be going to stay with him for two weeks in December. Jimmy has severe acne, and has just started a course of Roaccutane®. He is looking forward to scuba diving while there. Mrs Brown is on Cymbalta® for her depression. What malaria prophylaxis would you recommend for them?

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Introduction

Although worldwide, several groups are trying to improve the situation, malaria remains a serious threat to many people, both those living in endemic areas, and to travellers to these areas. People are infected with malaria through the bite of a female *anophelese* mosquito. Therefore, the best way to avoid malaria is to avoid being bitten by mosquitoes. This should always be emphasised. Even if chemoprophylaxis is advised, all measures to avoid being bitten by mosquitoes should be taken, as no chemoprophylaxis is 100% effective. These measures include the use of insect repellents, and only repellents containing N,N-diethyl-m-toluamide (DEET) or picaridin should be used.

In the past, when choroquine was still an effective antimalarial, making recommendations for malaria prophylaxis was relatively simple, as it had few genuine contraindications and drug interactions, and serious side-effects were rare. Unfortunately, the current situation is considerably more complicated. The recommended prophylactic options now have several contraindications, drug interactions, or side-effects. For these reasons, the choice of prophylaxis must be tailored to the individual. In addition, because none of the recommended options are without risk, it is very important to assess whether taking prophylaxis is necessary in the first place. Factors such as area, length of stay, time of the year, and type of accommodation, all play a role in making this decision.

Once the need for chemoprophylaxis has been confirmed, the task is then to choose the right option for the individual. Once again, the area to be visited, and length of stay will influence this decision, but the most important factors influencing this decision relate to the individual. This article will focus on some of these factors, and give guidance as to which prophylaxis is best suited to the situation, based on the guidelines for the prevention of malaria in South Africa, recently published on the Department of Health's website.

Any one of the following prophylactic is currently recommended for use:

- Mefloquine (weekly) (Lariam® or Mefliam®). Start at least one week before entering a malaria area, take weekly while there, and for four weeks after leaving the malaria area.
- Doxycycline (daily) (Doximal®, Cyclidox®, Dumoxin®). Start one day before entering a malaria area, take daily while there, and for four weeks after leaving the malaria area.
- Atovaquone-roguanil (daily) (Malanil®). Start one to two days before entering malaria area, take daily while there, and for seven days after leaving the area.

Some circumstances requiring careful consideration

Pregnant women

Pregnant women should avoid travelling to endemic malaria areas.[1] There is no prophylactic regimen that provides total protection against malaria, and malaria poses a significant risk to the health of both the mother and the foetus. Malaria increases the risk of stillbirth, miscarriage, neonatal death and maternal death.[1] Pregnant women are also more likely than non-pregnant women to suffer from severe malaria. This is especially true of the primigravidae. The mechanism

is unclear, but may be related to cellular immune function suppression. The greatest risk is that of spontaneous abortion.[2]

If travel to a malaria area is unavoidable, both meticulous non-drug measures and chemoprophylaxis are essential.

Mefloquine

Although the manufacturers contraindicate the use of mefloquine in pregnancy, the World Health Organization (WHO) and others recommend that mefloquine may be considered for chemoprophylaxis in women in their second or third trimester of pregnancy when visiting high-risk chloroquine-resistant *Plasmodium falciparum* areas. Cumulative evidence from clinical trials, and reports of inadvertent use of mefloquine during pregnancy, do not suggest an association with adverse foetal outcomes.[3-5]

The use of mefloquine in the second and third trimester has not been linked to increased congenital malformations.[5,6] Recent literature also suggests that mefloquine may be considered for chemoprophylaxis in women during their first trimester of pregnancy when visiting very high-risk chloroquine-resistant *P. falciparum* areas.[7] However, further studies are needed due to concerns about a possible increase in the occurrence of spontaneous abortion after use in the first trimester.[7]

Doxycycline

Doxycycline is contraindicated during pregnancy. Tetracyclines are human teratogens, and have been associated with the inhibition of skeletal development, foetal bone growth, and teeth dysplasia and discoloration.[5] Inadvertent exposure to doxycycline during pregnancy may not necessarily warrant therapeutic abortion.[2]

Atovaquoneproguanil

The safety of atovaquone and proguanil hydrochloride, when administered concurrently for use in human pregnancy, has not been established, and the potential risk is unknown.[8]

Recommendation

If it is necessary for a pregnant person to enter a malaria risk area, mefloquine, depending on the stage of pregnancy, and the malaria risk in the specific area, is recommended. In all cases, the use of very strict non-drug measures is advised. Pregnant women must be informed of the high risk to both themselves and their unborn baby, and if any malaria symptoms occur, should be told to seek medical attention immediately.

Breastfeeding mothers

Infants should not be taken to malaria risk areas as they are at a significantly higher risk of developing severe malaria.[4] If it is necessary for them to enter a malaria risk area, then breastfed, as well as bottle-fed, babies, must receive the full recommended paediatric doses of appropriate antimalarials. The amount of antimalarial agent excreted into breast milk is insufficient to provide the infant with adequate protection against malaria.[5]

Mefloquine

Mefloquine is contraindicated in breastfeeding mothers by the manufacturers, but the WHO guidelines state that it is safe to use.[1,9,10] Approximately four per cent of a single 250 mg mefloquine dose has been shown to be recovered from the milk. Although these amounts are not considered to be harmful to the nursing infant, the long-term effects of the drug, via breast milk, have not been studied.[11,12] The levels reached in the infant's drug levels are insufficient to provide adequate protection against malaria.[11]

Doxycycline

Doxycycline is excreted into breast milk in low concentrations, and may affect the breastfeeding infant adversely.[11] However, the American Academy of Paediatrics considers tetracycline to be compatible with breastfeeding.[11] The length of exposure to doxycycline from breast milk is a potential hazard to the infant.

Atovaquone-proguanil

Safety has not been established, and it is therefore not recommended.[1,13]

Recommendation

The WHO recommends mefloquine for breastfeeding mothers travelling to chloroquine-resistant malarial areas.[1] In addition, breastfed babies should receive the full recommended paediatric doses of the appropriate antimalarials.

Children

Children are at special risk as they can become seriously ill with malaria very rapidly. Babies and young children under the age of five years old should not be taken into malaria areas unless it is absolutely essential. Children must be protected against mosquito bites at all times, and mosquito nets must be used to cover bedding. It is advisable to keep babies under mosquito nets for as long as possible between dusk and dawn.[4]

When a child develops a febrile illness, either while in a malaria area, or after having left the area, medical help must be sought immediately. Symptoms of malaria in children may not be typical, and therefore malaria should always be suspected. In infants, malaria should even be suspected in non-febrile illness.[4]

Antimalarial drugs must be kept out of reach of children, and preferably stored in childproof containers.

Mefloquine

Mefloquine can be used in children over three months of age, or in those weighing over five kilogrammes. The dose is based on the weight of the child.[5,9]

Doxycycline

Doxycycline should not be used for prophylaxis in children under eight years of age because of the risk of staining permanent teeth, and inhibiting bone growth.

Atovaquone-proguanil

Due to lack of data, this combination is not recommended for children weighing less than 11 kg.[1]

Paediatric tablets are now available for children who weigh between 11-40 kg.

People with epilepsy

Selecting a chemoprophylactic agent for an epileptic patient is problematic. Some of the agents have been reported to cause convulsions, and others may interact with anti-epileptic medication. Epileptic patients must use non-drug measures diligently to protect themselves against mosquito bites. They must also be warned about the possible risks of taking chemoprophylactic agents, and of contracting malaria, to allow them to make an informed decision.

Mefloquine

Mefloquine is contraindicated for malaria prophylaxis in patients with a history of convulsions.[9] Several case reports have been reported of first-time seizures in patients taking mefloquine in prophylactic doses.[5,14]

There have also been reports of mefloquine reducing the half-life, and lowering the blood levels of the anticonvulsant, sodium valproate.

Doxycycline

Doxycycline does not affect epilepsy, but may interact with some of the anticonvulsants. Carbamazepine, phenytoin and barbiturates may shorten the half-life of doxycycline by up to 50%, thus potentially compromising its therapeutic efficacy. The degree to which the levels are affected is not clear, and an exact recommendation cannot be made because there is limited experience with an increased prophylactic dose. Increasing the doxycycline dose may also result in an increased incidence of side-effects.[3,5,15]

In summary, epileptic patients who are not taking carbamazepine, phenytoin or barbiturates, can safely use doxycycline as prophylaxis. However, patients taking these must be made aware of the fact that the normal dose of doxycycline may not provide adequate protection, and that increasing the dose may result in increased risk of side-effects.

Atovaquone-proguanil

The guidelines for malaria prevention for United Kingdom travellers recommend this combination as suitable for people suffering from epilepsy, who also require malaria prophylaxis.[16] Although currently there is insufficient published information on its use in people with epilepsy, epilepsy is not listed as a contraindication or precaution.

Recommendation

Doxycycline is an option for epileptics with the above proviso.

Atovaquone-proguanil has also been used.

People with psychiatric problems

Going on holiday and having a change of scenery may be particularly beneficial for the stressed or depressed individual. However, careful consideration must be paid to choosing appropriate prophylaxis for those with mental illness of any kind.

Mefloquine

Mefloquine has been reported to cause serious neuropsychiatric symptoms in approximately one in 10 000 users. Symptoms can develop as early as the first week of use, and more than 75% of the adverse reactions are apparent by the third dose. In most cases, symptoms resolve within three weeks of stopping taking the drug, but there are reports of symptoms persisting for some months, and even years, in a small number of cases.[17] Reported side-effects include depression, anxiety, acute psychotic episodes, subtle mood changes, insomnia, strange dreams, and depersonalisation. Therefore, mefloquine is contraindicated in individuals with a present, or prior, history, of any central nervous system (CNS) disorder.[9]

Doxycycline

Doxycycline may occasionally cause dizziness, headaches. blurred vision and nausea, but psychiatric adverse effects are extremely rare.

Atovaquone-proguanil

Although there is no specific information on the use of atovaquone-progaunil in individuals with a CNS disorder, the side-effect profile does not indicate that there would be a problem.[1,8]

Recommendation

Doxycycline and atovaquone-proguanil are the safest options for patients with psychiatric symptoms who require malaria prophylaxis.[14,17]

People on anticoagulant therapy

Patients on anticoagulant therapy should avoid travelling to malaria areas where chemoprophylaxis is indicated. Malaria chemoprophylaxis is very difficult in these patients, especially as monitoring of international normalised ratio (INR) is particularly challenging when travelling in endemic malaria areas. Both bleeding and clotting, which can occur when trying to regulate the INR, can be very dangerous. Thus, the use of strict non-drug measures in those travelling to low-risk malaria areas should be vigorously encouraged, and visits during the high-risk malaria season, or in high-risk malaria areas, actively discouraged. If travel to these areas is essential, patients should be fully informed, both about the potentially life-threatening risks of malaria, and about the potential of chemoprophylaxis to interfere with their anticoagulation, which may increase their risk of bleeding or clotting.

Recommendation

Mefloquine is the only chemoprophylaxis option that can be considered for these patients, as both doxycycline and atovaquone-proguanil may potentiate the effect of oral anticoagulants. However, there are insufficient data on the safety of mefloquine in such patients, so prophylaxis should be started three-to-four weeks before travel to monitor INR closely for the possibility of an interaction.

People with porphyria

Mefloquine

Appears to be well tolerated.[18]

Doxycycline

Avoid use, as doxycycline has been associated with acute attacks of porphyria.

Atovaquone-proguanil

Proguanil is known to be safe in porphyria, and atovaquone is considered to be safe as it is not significantly metabolised.[18]

Recommendation

Either mefloquine or atovaquone-proguanil can be used.

People with diabetes

Mefloquine

There is insufficient information on the use of mefloquine in diabetes. Blood glucose levels should be monitored.

Doxycycline

Doxycycline may increase the hypoglycaemic effect of insulin. Blood glucose levels should be monitored.

Atovaquone-proguanil

There are no known problems. It is recommended that blood glucose levels are monitored.

Recommendation

Any of the regimens can be used, but blood glucose levels should be monitored.

People with renal insufficiency

Mefloquine

There is a lack of safety data, and mefloquine should be used with caution.

Doxycycline

Doxycycline is unaffected, and can be used safely.

Atovaquone-proguanil

Atovaquone-proguanil is contraindicated in severe renal failure (creatinine clearance < 30 ml/min).[8]

Recommendation

Any of the regimens can be used in mild-to-moderate renal insufficiency, but atovaquone-proguanil is contraindicated in severe renal failure.

People with hepatic impairment

Mefloquine

Elimination of mefloquine may be prolonged, resulting in higher plasma levels. It is contraindicated in severe impairment.

Doxycycline

Doxycycline should be administered with caution to hepatically-impaired patients, or those receiving hepatotoxic drugs. Doxycycline may be partially metabolised in the liver, and impairment may lead to an increase in plasma levels.

Atovaquone-proguanil

Atovaquone-proguanil is safe to use in mild-to-moderate hepatic impairment, but there are no data on its use in severe hepatic impairment.[8]

Recommendation

Any of the regimens can be used in mild-to-moderate impairment, but in severe impairment, mefloquine is contraindicated, and the others should be used with caution.

The immunocompromised patient

Immunocompromised patients, e.g. human immunodeficiency virus (HIV) positive patients, those on long-term steroids, those who have had a splenectomy, and patients receiving chemotherapy, and their doctors should weigh up the risks very carefully before entering a malaria area. Factors such as the degree of immunosuppression, malaria risk in the area being visited, and availability of medical resources, should be taken into account.

Recent studies have shown that HIV-infected patients have a higher prevalence of parasitaemia, and are more likely to get severe malaria. Additionally, acute malaria may increase HIV viraemia. These studies were carried out in endemic areas among HIV-positive patients who were not taking antiretrovirals (ARVs). The relevance of this in HIV-infected travellers taking ARVs is not known.[19]

If immunocompromised patients cannot avoid travel to malaria areas, the most effective chemoprophylaxis should be used, and extremely strict non-drug measures should be followed. Drug interactions with concurrent medication should also be carefully considered, especially in patients taking immunosuppressants after organ transplants.

Travellers on antiretroviral therapy

It is a reasonable presumption that, since the introduction of ARVs, HIV-infected persons are more able, and likely, to travel, than previously. Although they may no longer be at as high a risk of contracting other diseases as before, there is potential for interactions between their ARVs and other medications that are required, such as vaccines and malaria chemoprophylaxis.

There is a paucity of current data on potential interactions between antimalarials and ARVs, but practical experience has not indicated a high risk of toxicity, or serious adverse events, when combining these two categories. The major concern regards the protease inhibitors, as they are inhibitors of the cytochrome P450 enzyme system. This may affect mefloquine or atovaquone, although it has not been proved clinically, but, as doxycycline is not significantly metabolised by the liver, it is not affected.[19]

Theoretically, efavirenz, nevirapine and the protease inhibitors, may reduce the level of mefloquine, but this has not been shown to be clinically significant.[19-21] In theory, the protease inhibitors may also reduce atovaquone levels, while indinavir levels may be reduced by atovaquone-proguanil.

Zidovudine levels may be increased by atovaquone-proguanil.

There are no known interactions with tenofovir, emtricitabine lamivudine, stavudine or didanosine, and the recommended antimalarials.

In vitro studies have shown that protease inhibitors inhibit the growth of *P. falciparum*.[19]

Recommendation

Currently, doxycycline is the recommended option for malaria prophylaxis in HIV-infected travellers on ARVs, as there are no known drug interactions with any of the ARV regimens.[19] Atovaquone-proguanil is currently not recommended as the first-line choice because of limited documentation regarding drug interactions, and there is potential for reduced levels of mefloquine in patients taking certain ARVs.

Any malaria prophylaxis with a potential for an interaction with the traveller's ARVs must be started several weeks prior to departure, in order to permit measurement of plasma levels.[19]

People involved in activities requiring fine co-ordination and spatial discrimination

Mefloquine

Mefloquine can cause dizziness, a disturbed sense of balance, and neuropsychiatric reactions during, and up to, three weeks after its use. Therefore, caution must be exercised when driving and operating machinery, while taking this drug.[9] The WHO recommends that piloting of aircraft and deep-sea diving should be avoided while taking mefloquine.[1]

Although the latest studies do not reflect any significant effects of mefloquine on fine motor coordination, it is prudent to exercise caution when considering giving it to persons operating machines, driving, deep-sea diving, or flying.[4] The drug may cause sleep disturbances, which in the long term, may affect coordination.

Doxycycline

Using doxycycline in this situation does not appear to cause any problems.

Atovaquone-proguanil

Atovaquone has no adverse psychomotor effects on aircrew.[16] Based on the pharmacology of atovaquone and proguanil, with regard to driving and operating machinery, a detrimental effect is not expected.[8]

Recommendation

Doxycycline or atovaquone-proguanil may be considered as prophylactic options.

People taking doxycycline for acne

One of the many drugs used to manage acne is oral doxycycline. For malaria prophylaxis, doxycycline is administered as a single daily dose of 100 mg, starting one to two days before entering the area, taken daily while in the area, and continuing for four weeks after leaving the area.[1]

Recommendation

A person who is already taking doxycycline for acne need only ensure that the daily dose of doxycycline is equivalent to that recommended for malaria chemoprophylaxis.

If a patient is taking another tetracycline, such as minocycline, for acne, an option is to replace it with doxycycline in the recommended doses for malaria chemoprophylaxis. There is insufficient data to support the use of minocycline for malaria prophylaxis, and there is a possibility of an increase in adverse reactions at the required dose.

People already on chloroquine therapy

Mefloquine

Mefloquine should not be taken concurrently with chloroquine because of the danger of toxic cardiac or CNS reactions.[22]

Doxycycline

Doxycycline is an option for these patients entering chloroquine-resistant areas.

Atovaquone-proguanil

There is no documented interaction between atovaquone and chloroquine, and although proguanil and chloroquine can increase the incidence of mouth ulcers, they were previously given together. Therefore, there is no reason why atovaquone-proguanil cannot be used in patients who are already taking chloroquine.

Recommendation

Either doxycycline, or atovaquone-proguanil, can be taken by people who are already taking chloroquine for another condition.

Changing from one chemoprophylactic to another

It may be necessary to change from one antimalarial agent to another after starting the course, if side-effects develop.

Recommendation

Patients changing from doxycycline to mefloquine or vice versa, may do so without a washout period. Currently, there are no data on changing from atovaquone-proguanil to doxycycline or mefloquine, or vice versa. Bear in mind that the former two act as blood schizonticides (only once the parasite enters the blood cells), while the latter acts as a tissue schizonticide much earlier in the malaria cycle.

Long-term chemoprophylaxis for people travelling for extended periods

As with all recommendations, the advice for travellers requiring long-term chemoprophylaxis must be individualised according to their specific circumstances. The risk of contracting malaria is roughly proportional to the length of stay in a malaria area. Therefore, the longer the stay, the more important it is to use a highly effective chemoprophylactic regimen.[16]

Restricting long-term use of any of the regimens is due to lack of data, rather than any evidence of new toxicity problems resulting from long-term use.[16]

Most adverse events from the use of antimalarials tend to occur shortly after the first few doses, and the incidence of late-onset events is very low.[16]

Mefloquine

The Centers for Disease Control (CDC) has recommended that mefloquine can be used for long-term malaria chemoprophylaxis.[23] The advisory committee on malaria prevention for UK travellers, believes that, in the absence of problems in the short term, mefloquine can be used for up to three years.[14] Long-term use of mefloquine does not appear to relate to increased side-effects.

Doxycycline

Experience with doxycycline use for periods exceeding six months is limited, but evidence suggests that it may be taken safely for periods of up to two years.[1,3,7] There is no evidence of harm resulting from long-term use.[13] However,

ideally, doxycycline should be taken by individuals who will be exposed to malaria for short periods of time.[23]

Atovaquone-proguanil

Although both components have been used individually on a long-term basis, there is limited data concerning long-term use of atovaquone-proguanil.[13] In South Africa, this combination is registered without a restriction on the length of the course.[8]

People who have grown up in an endemic malaria area, and who may have developed immunity, will lose this immunity within a year or so of being out of the malaria area.[22] These individuals must take the necessary precautions when re-entering or visiting a malaria area.

Recommendation

Mefloquine is generally the antimalarial of choice for long-term use, and atovaquone-proguanil, the choice for short-term travel, but all the other factors need to be taken into consideration.

If we have a look at the case scenario mentioned at the beginning, we can now make recommendations:

- Depending on what Mr Brown is doing on the construction site, he can either take doxycycline (if he is working with machinery, and requires fine motor coordination) or mefloquine. It is not financially viable to take atovaquone-proguanil for that length of time.
- Mrs Brown must not take mefloquine, as she is suffering from depression, but she can take either doxycycline or atovaquone-proguanil.
- Jimmy, their son, cannot take doxycycline as he is on Roaccutane® (isotretinoin), and with this combination, there is a potential for pseudotumour cerebri. He should also not take mefloquine if he is going to dive, so his only option is to take atovaquone-proguanil.
- Julie is only four years old, and so cannot take doxyycline or atovaquone-proguanil. She must take mefloquine, and must remember to start it at least a week before going to Mozambique.

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