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A Narrative Review of Use of Drugs for Prevention of Malaria

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ABSTRACT

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An estimated 3.4 billion people are at risk of malaria. The use of drugs for prevention of malaria among people at risk of the disease has been practiced since centuries in the form of chemoprophylaxis, intermittent preventive treatment (IPT) or Mass Drug Administration (MDA). Articles were retrieved using search from Cochrane database of Systematic reviews and Google search. Keywords used included "malaria chemoprophylaxis"," Drugs for prevention of Malaria" and "guidelines for prevention of Malaria". Chemoprophylaxis is an effective strategy for a limited time but it does not offer lifelong protection. The 6 drugs in the WHO guidelines for chemoprophylaxis of Malaria are Atovaquine Proguanil combination, Chloroquine, Chloroquine- Proguanil combination, Doxycycline, Mefloquine and Proguanil. The guidelines for India recommend Doxycycline for short stay and Mefloquine for longer stay. Regimens recommended for use in South Africa include Mefloquine, Doxycycline or Atovaquone-proguanil. Though MDA has gone into disrepute because of its ability to produce drug resistance, examples of successful elimination using MDA exist. IPT given to women in first and second pregnancies reduced the number of women with severe anaemia, perinatal deaths and increased the birth weight of babies. WHO recommended IPT for children consists of Sulfadoxine-Pyrimethamine and Amodiaquine given to children between 3-59 months. Reviews of IPT in children show benefits in reducing the number of malaria episodes and preventing severe disease and deaths. IPT in infants show 30% reduction in incidence. More research is required in prevention of malaria for bringing less costly drugs with limited side effects. Priority should be given to the use of non pharmacological measures to reduce the burden of disease, so that we can prevent the need for using drugs for prevention of malaria.

Keywords: Malaria, Prevention, Chemoprophylaxis, Intermittent Preventive Treatment, Mass Drug Administration

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INTRODUCTION

An estimated 3.4 billion people are at risk of malaria. Of this total, 2.2 billion were at low risk (<1 reported case per 1000 population), of whom 94% live in geographic regions other than the African Region. The 1.2 billion at high risk (>1 case per 1000 population) live mostly in the African Region (47%) and the South-East Asia Region (37%). Due to increased global investment and action on malaria control, substantial progress has been made since 2000.[1] A number of factors determine the risk of acquiring malaria infection. These include the intensity of transmission in the area, the length of stay in the area, the time of year (in areas of seasonal malaria transmission), the inclusion of an overnight stay (as transmission occurs between dusk and dawn), the prevalence of drug resistant malaria in the area, the susceptibility of the host (High risk groups include non-immunes, pregnant and breast-feeding women, young children, comorbid disease, splenectomised and immunocompromised patients, the presence of comorbid disease and concurrent medications, the type of accommodation (e.g. air conditioned rooms, camping) and access to medical care . The risk of malaria transmission varies greatly according to the specific destinations within a defined geographic area. While the risk of malaria is much less at altitudes above 1500 metres, disease can occur in hot climates at altitudes of up to 3000 metres.[2,3]

The use of drugs for prevention of malaria among people at risk of the disease has been practiced since centuries. The empiric use of antimalarial drugs to prevent malaria can be generally grouped into three categories: 1) chemoprophylaxis, where drugs are administered at suppressive doses throughout the defined period; 2) intermittent preventive treatment (IPT), where a full curative dose of an antimalarial is given to a target population at specified times; or 3) MDA, where drugs are administered to the whole population

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either using full therapeutic courses, known as direct MDA, or through the fortification of dietary salt, known as indirect MDA (the Pinotti method).[4,5] A large number of good reviews exist on the prevention of malaria using drugs. This narrative review tries to summarise them.

METHODS

Initial search was done in the Cochrane database of systematic reviews. The keywords used for search were "malaria chemoprophylaxis". Five results were obtained. Out of them, one was not in English and hence excluded. Another article was on vaccines in pregnant women for tetanus, which described the need for studying the interaction of these vaccines with chemoprophylaxis of malaria. This was also excluded. There were three major results. First the abstracts were gone through, then the full texts and then retrieved articles from "more like this" section. Google search was also done using the search term "Drugs for prevention of Malaria" and "guidelines for prevention of malaria".

RESULTS

Malaria chemoprophylaxis

If an individual is travelling to a malaria area, it is important to determine whether he or she requires chemoprophylaxis, or whether adequate protection can be provided by the regular use of personal protection measures. The decision as to whether chemoprophylaxis is necessary is complex. It depends on the areas to be visited and the risk that the traveller has of being exposed to mosquitoes and of developing malaria. The greater the traveller's risk of contracting malaria and developing complications, the greater the need for chemoprophylaxis. People at highest risk of developing severe malaria complications include the elderly, babies and young children (< 5 years), pregnant women and immunocompromised individuals (e.g. patients living with HIV and AIDS, those who have had a splenectomy, and patients receiving long-term steroids or chemotherapy).

Chemoprophylaxis is an effective strategy for a limited time (ranging from a few weeks to a few years). However, it does not offer lifelong protection because of the high costs and the potential for development of drug resistance.[6]

Malaria infects 10,000 to 30,000 international travellers each year. A Cochrane review was done to assess the efficacy, safety, and tolerability of atovaquone-proguanil, doxycycline, and mefloquine compared to each other, and also when compared to chloroquine-proguanil and to primaquine. Eight trials with 4240 participants were obtained. Overall the evidence base was small, and there was no evidence to support the use of primaquine. There was only limited evidence on which of the three currently available drugs is most effective in preventing malaria. While none of the eight trials reported any serious adverse events, all trials reported common adverse events from antimalaria drugs. Atovaquone-proguanil and doxycycline were well tolerated by most travellers, and they are less likely than mefloquine to cause neuropsychiatric adverse events. Chloroquine-proguanil caused more gastrointestinal adverse events than other chemoprophylaxis. In other respects, the common unwanted effects of currently available drugs are similar. Another 22 published case reports of deaths, including five suicides, associated with mefloquine use at normal dosages. No other currently used drugs were reported as causing death, at normal dosages.[7]

Guidelines

WHO guideline emphasize that travelers and their doctors should be aware that no antimalarial prophylactic regimen gives complete protection, but good chemoprophylaxis (adherence to the recommended drug regimen) significantly reduces the risk of fatal disease. The following should also be taken into account: 1) Dosing schedules for children should be based on body weight. 2) Weekly chloroquine should be started 1 week before arrival. 3) Weekly mefloquine should preferably be started 2–3 weeks before departure, to achieve adequate drug blood levels and to detect possible side-effects before travel so that possible alternatives can be considered. 4) Daily prophylaxis with doxycycline or atovaquone–proguanil should be started 1 to 2 days before arrival (or earlier if drug tolerability needs to be checked before departure) **(Table 1).**

According to the guidelines for India[8] Chemoprophylaxis should be administered only in selective groups in high P.falciparum endemic areas. Use of personal protection measures is encouraged for pregnant women and other vulnerable population including travelers. However, for longer stay of Military and Para-military forces in high Pf endemic areas, the practice of chemoprophylaxis is to be followed wherever appropriate. For Short term chemoprophylaxis (up to 6 weeks) Doxycycline, is the drug of choice. Chemoprophylaxis for longer stay (more than 6 weeks) is with Mefloquine. Regimens currently recommended for use in South

Table 1. WHO guidelines for chemoprophylaxis[3]

Generic name	Dosage regimen	Duration of prophylaxis	Pregnancy	Breast Feeding	Children	Main Contraindication
Atovaquine Proguanil combination	1 dose daily >40kg – 1 adult tablet (250 mg atovaquine and 100mg proguanil) 11-20kg – paediatric tablet (1/4th dose of adult) 21-30kg : 2paediatric tablet 31-40 kg: 3 paediatric tablet	Start 1 day before departure to 7 days after return	No data, Not recommended	No data, not recommended	Not recommended in <11kg	Hypersensitivity Renal insufficiency (creatinine clearance <30ml/mt)
Chloroquine	5mg base/kg weekly one dose or 10mg base/kg weekly divided in 6 daily doses Adult – 300mg weekly or 6 daily doses of 100mg with one drug free day	Start 1 week before departure to continue till 4 weeks after return. If daily dose start 1 day before departure	Safe	Safe	Safe	Hypersensitivity, history of epilepsy, psoriasis
Chloroquine-Proguanil Combination	>50kg – 100mg chloroquine base plus 200mg proguanil	Start 1 day before departure to 4 weeks after return	Safe	Safe	Tablet size not suitable for <50kg	Hypersensitivity, history of epilepsy, psoriasis, Liver or renal insufficiency
Doxycycline	1.5mg salt/kg daily Adult dose: 1 tablet 100mg daily	Start 1 day before departure to 4 weeks after return	Contraindicated	contraindicated	Contraindicated under 8 years of age	Hypersensitivity to tetracyclines, Liver dysfunction
Mefloquine	5mg/kg weekly Adult dose :1 tablet 250mg weekly	Start 1 week before depature to continue till 4 weeks after return	Not recommended in first trimester because of lack of data	Safe	Not recommended under 5kg because of lack of data	Hypersensitivity to Mefloquine, psychiatric (including depression) or convulsive disorders. History of severe neuropsychiatric disease, concomitant halofantrine treatment, treatment with mefloquine in previous 4 weeks, not recommended for people performing activities requiring fine coordination
Proguanil	3mg/kg daily Adult dose : 2 tablets of 100 mg daily	Start 1 day before depature and continue for 4 weeks after return	Safe	Safe	Safe	Liver or kidney dysfunction

Africa (2009), include Mefloquine, Doxycycline or Atovaquone-proguanil.[9]

Guidelines from the Health Protection Agency Advisory Committee on Malaria Prevention (ACMP) in UK travelers (2007) recommend Mefloquine, or Doxycycline or Atovaquone/Proguanil for travel to high risk areas of Bangladesh and India. Chloroquine plus proguanil is recommended as an alternative. For travel to areas where the risk is variable, the latter is recommended and the former options are kept as alternative. Only awareness of risk and protection from mosquito bites is recommended for travel to low risk areas.[10]

CDC recommends the use of drug according to the country of travel as per the yellow book. They provide reasons for recommending use and nonuse of drugs.

Mass Drug Administration

The administration of drugs against malaria to whole populations, termed mass drug administration (MDA), was a component of many malaria elimination programmes in the 1950s. MDA can be given on more than one occasion. The objective of MDA is to reduce the burden of clinical malaria.[4] A Cochrane review assessed the impact of MDA on several malaria-specific outcome measures. Thirty-two studies were included in this review, from sites in Asia, Africa, Europe and the Americas. It found that although MDA can reduce the initial risk of malaria-specific outcomes, these reductions are not sustained. However, a few studies showed sustained impact more than six months after MDA. Adverse events were inadequately addressed in most studies. Notable severe drug reactions, including haemolysis, haemoglobinuria,

severe anaemia and death, were reported with 8-aminoquinoline plus schizonticide drug co-administration, while severe skin reactions were reported with sulphadoxine-pyrimethamine plus artesunate plus primaquine.[11] MDA has been into disrepute for its ability to produce drug resistance.[12] A large study conducted in Nigeria showed that several rounds of MDA combined with intensive vector control did not interrupt transmission.[4] However examples of using MDA for successful elimination of malaria exist in islands of Aiyetun and Cambodia.[13,14] Elimination of P. vivax is considered to be more challenging than P. falciparum and newer drugs may be required.[4]

Malaria chemoprophylaxis for pregnant women

Women living in malarial areas and who are pregnant for the first or second time are more likely to become infected with malaria. This brings severe anaemia causing weakness and tiredness for the mother, and slows the growth of the baby. A Cochrane review identified seven trials which gave malaria prophylaxis to all pregnant women. The objective of the review was to assess drugs given to prevent malaria infection and its consequences in pregnant women living in malarial areas. This included prophylaxis and intermittent preventive treatment (IPT).[15] Intermittent preventive treatment (IPT) is the administration of a full course of antimalarial treatment to a population at risk of malaria during a specific time period, regardless of whether or not they are known to be infected.[16] These did not show any benefit to either the mother or the babies. However another review of 6 trials which gave antimalaria chemoprophylaxis to women in their first and second pregnancies found beneficial effects in terms of reducing the number of women with severe anaemia, increasing the birth weight of the baby and reducing perinatal deaths. The effect of the drug administration to the development of resistance was not assessed.[15]

IPT policies were first implemented in pregnant women (IPTp), as an alternative to chloroquine. The treatment consisted of a single dose of sulphadoxine/pyrimethamine (SP) given two or three times during the pregnancy.[17] IPT was introduced because of the unpopularity of chloroquine chemoprophylaxis and drug resistance.[4] IPT with SP is recommended by WHO for all pregnant women resident in areas with a moderate or high level of malaria transmission.[18]

Malaria chemoprophylaxis for children

In areas where malaria is common, young children have repeated episodes of malarial illness, which can sometimes be severe and life-threatening. In areas where malaria is seasonal, a practical policy option is to give drugs to prevent malaria at regular intervals during the transmission season, regardless of whether the child has malarial symptoms or not. This is known as Intermittent Preventive Treatment (IPTc).

A Cochrane review identified seven trials (12,589 participants); all were conducted in West Africa, and six of seven trials were restricted to children aged less than 5 years. The results show IPTc prevents three quarters of all malarial episodes, including severe episodes, and probably prevents some deaths. Several antimalarial drugs or combinations have been tried, and shown to be effective. The most studied is amodiaquine plus sulphadoxine-pyrimethamine (AQ+SP). This combination probably doesn't have serious side effects but does cause vomiting in some children.[19]

Among children, infants are an important target for prevention using drugs. The WHO also recommends intermittent preventive treatment in infants (IPTi) up to the age of 12 months. It should be administered together with the second and third diphtheria-pertussis-tetanus (DPT) and measles vaccination in areas that have a moderate to high transmission rate of malaria.[20,21] Vaccination provides a good opportunity for easy delivery of this service. 30% reduction in the incidence of clinical malaria with a variable impact on the incidence of anaemia and hospital admissions has been reported with IPTi.[22] No impact on mortality was detected.[4]

Currently, the WHO recommends seasonal malarial chemoprevention (SMC) or IPTc, in seasonal malarial areas during the transmission season.[23] This consists of a complete treatment course of SP and amodiaquine (AQ), given to children between 3-59 months, at monthly intervals, during the high risk period of malaria transmission. Children may receive up to four doses of this antimalarial treatment during the malarial transmission season with the aim of maintaining therapeutic drug levels during the period of high transmission. This strategy excludes areas with SP resistance outbreak.[24]

Special situations

Sickle cell anaemia:Malarial infections in people with sickle cell anaemia trigger the development of sickle cell crisis. So it is important to prevent malaria in them. A review conducted by the Cochrane, to look into the effectiveness and adverse effects yielded 2 small trials in 223 persons. It showed that benefit in terms of reducing the number of sickle cell crisis,

blood transfusions, hospital admissions, and increasing the mean haemoglobin levels, but they did not collect data on potential adverse effects. More research is needed, therefore, to be sure of the benefits and to assess possible problems of drug resistance, and other potential long-term adverse effects that may be associated with continuous treatment.[25]

LIMITATION

Quality of studies and articles were not assessed systematically for inclusion and exclusion.

CONCLUSION

Drugs are not as effective as vaccines as a method of prevention of malaria because it has to be taken for long periods of time. Stringent non-drug measures should be taken to avoid mosquito bites throughout the year, even in areas of low malarial transmission intensity. In addition, effective drugs should be taken whenever and wherever the risks of acquiring malaria exceed the probability of experiencing a serious adverse reaction to the drug regime. More research is required in prevention of malaria for bringing less costly drugs with limited side effects. We also need to look at ways in which we can reduce the burden of the disease to such an extent that the use of drugs for prevention of malaria may no longer be required.

END NOTE

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