

Chapter - 13
MALARIA CHEMOPROPHYLAXIS
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INTRODUCTION

Protection against malaria infection has two major aspects: personal protection against mosquito bites (repellents, bednets, personal outfit etc) and the use of chemoprophylactic drugs. The former is being increasingly recommended in traveller's advice and used in control strategies against the infection; the latter is frequently and passionately debated.

While in endemic areas only selected groups in specific situations will use chemoprophylaxis, any tourist visiting these areas should use one or a combination of prophylactic drugs together with the above mentioned measures against mosquito bites. This is a controversial field: what drugs for which areas, who should take them and for how long, what are the indications and counterindications, the incidence of serious side effects; these questions are frequently discussed. In general and whatever the strategy, it is advisable for all travellers to malaria infested areas to protect themselves but the same cannot be said for the resident population in endemic areas where clear selection of population groups is mandatory for major drawbacks can be expected from a non-selective attitude. In these countries the choice of a particular drug will be limited, because their national policies will decide which drug is used for chemoprophylaxis.

Statistical data from the World Tourism Organization at the beginning of this decade showed that nearly 30 million people from non malaric countries visit malaria endemic areas yearly¹. The matter is therefore of major importance in terms of international health. Although the caucasian tourist seems to be the main target group for chemoprophylaxis, other ethnic groups with years of residence in Europe or the US, who go and visit relatives in malarious areas increasingly appear in statistics of imported malaria in the developed world². In many countries a high percentage of travellers seek health advice from their travel agencies^{3,4} which usually tends to minimize the risks. Surveys carried out at different european airports show that travellers leave their countries with poor information (if any) about malaria prophylaxis. A major effort is needed for updating the training of general practitioners and travel clinics personnel. For the new generations, international health should find its place in medical schools and spark an awareness of these problems in future young doctors and other health personnel.

PROTECTION AGAINST MOSQUITO BITES.

From a practical point of view, a tourist visiting endemic areas for short periods should protect himself with mosquito repellents and bednets, while the local population should ideally be protected with impregnated bednets.

1- Mosquito Repellents. Synthetic pyrethroid coils give out an effective smoke during an 8 hs. period, but concern is growing about the potential lung damage inflicted after prolonged exposures. The spraying of walls and ceilings, for years a major asset of the anti malaria national campaigns, is less used nowadays, for purely economic reasons because residual insecticides such as DDT have still a place in fighting mosquito in the home rooms and are harmless to humans⁵. DDT application in agriculture is more controversial.

2- Bednets. Bednets impregnated with the pyrethroid insecticides can last for about six months⁶. Their effect on morbidity and mortality of children was well proved through a controlled trial in the

Gambia⁷ and has been confirmed since then by many authors in different geographic and social settings. Considered by many as the best and more reliable tool for controlling malaria at present. Keeping the bednets effective requires minimum care activities: if not repaired they end up being real mosquito traps, if washed they will lose part of its repellent potential. Therefore the active involvement of individuals and of the community as a whole is required for any bednets programme to be successful.

3- Repellents. Vapour released from commercial tablets or coils are effective when used in enclosed places but of doubtful effect when used at the open air. In Kenya, local herbs used by villagers have been found to be as effective as the commercial coils⁸.

Di-ethyl toluamide is the most used type of chemical repellent. It is more effective in its alcohol solution with concentrations ranging between 25 and 50%. It has to be applied in the areas where most mosquitoes bite: low third of inferior extremities and the uncovered body areas.

CHEMOPROPHYLAXIS FOR THE LOCAL POPULATION IN ENDEMIC AREAS.

The use of chemoprophylaxis for residents in endemic areas is justified in three obvious at risk situations (infants, pregnancy and especially primigravidae, and the returning migrants) where the risks of not giving malaria protection will be too high.

1- In infants and young children in whom malaria is potentially lethal, directly (cerebral malaria) or indirectly (severe anaemia). No immunity or partial immunity is directly related to the clinical severity present in those cases. It has been rightly pointed out⁹ that more work is needed to evaluate whether the beneficial effects of chemoprophylaxis on the infant, are outweighed by a reduction of transplacental transfer of IgG. On the other hand the potential rebound effect after stopping chemoprophylaxis in infants has been shown to be true in terms of increase in the number of clinical attacks but there was no detectable effect on mortality¹⁰. Despite the difficulties of sustainability for achieving a wide coverage of those at risk groups, the many arguments in favor of chemoprophylaxis outweigh those against.

As during the malaria attack, iron reduced absorption and sequestration occur the infection contributes to anaemia in this age group. It has been shown that combining both chemoprophylaxis and insecticide treated bednets reduces the malaria infection as well as the number of anaemia cases. This approach is most advisable when feasibility is present, as it could reduce considerably the number of blood transfusions given at that age group in many tropical countries.

2- Pregnant women and especially primigravidae from endemic areas have a higher incidence of anaemia and clinically severe malaria, but this incidence is reduced in women taking antimalarials¹¹. However, specific IgG levels in pregnant women are not different in those with or without chemoprophylaxis. Targeted chemoprophylaxis is now recommended in pregnancy situations such as primigravidae and anaemic women¹² as well as the grand multigravidae with more than five pregnancies¹³. In endemic areas the use of chemoprophylaxis during pregnancy will determine the outcome. In this way there will be a significant reduction of low weight children, abortions and placenta previa. In the case of primigravidae, infant mortality can be reduced by a 50% (Greenwood 1989).

3- Migrants to zones of high endemicity coming from countries with no malaria (foreign residents) or from areas of the same country with a low prevalence of malaria. In both cases the situation of practically no immunity, parallels these groups with the caucasian travellers as to the risk of acquiring malaria.

General Considerations.

Provided the malariometric data of the area are well defined, the pros and cons of the strategy have been weighed and a reasonable network of health workers is available for the distribution of this prophylaxis, mortality and morbidity of this infection can undoubtedly be considerably reduced. A strategy of wide distribution is likely to produce major drawbacks¹⁴.

Sustainability in terms of economy and drug delivery is a serious obstacle and if restrictions are to be implemented group 3 (migrants) will receive a lower priority than infants and primigravidae. In those groups, the safer and cheapest drugs are used at MCH clinics, i.e. Chloroquine or Paludrine or both, in order to facilitate massive distribution to those groups. By restricting chemoprophylaxis to those selected groups, the drug pressure over the parasite is reduced and resistance is less likely to form^{15, 16}. Dosage of these and other drugs are presented in the following:

Table I. Main chemoprophylactic drugs used in Malaria prevention

D O S A G E ADULTS	DRUG
Chloroquine (Cl)	300 mgs./week (5mg/kg.)
Proguanil (P)	200 mgs./day °
Cl. + P.	300mgs./wk + 200mgs/day °
Dapsone(DDS)+Pyrimethamine	(100mg. + 12.5mgs)per week °
Doxycycline*	100 mgs/day °
Mefloquine*	250 mgs/week °

* Not to be used in pregnancy nor in children less than 8 years of age.

Table II. CHEMOPROPHYLAXIS FOR CHILDREN. AVAILABLE DRUGS.

DRUG	DOSE	OBSERVATIONS
Cloroquine	5mg/kg of base product	Syrup available in some countries
Proguanil tabs:100mg.	50mg/day:6/14kg 75mg/day:15/29kg	To be taken together a weekly
Cloroquine	100mg/day:30/40kg	in indicated areas.
Mefloquine tabs:250mg *	15/19kg: 1/4 Tab. 20/30kg: 1/2 Tab. 31/45kg: 3/4 Tab.	Single weekly dose only if weight>15 kg
Doxicicline tabs100mg*	2mg/kg /day	Only if > 8 ys. in multiresistant zones
Pyrimethamine	0.2 mg/kg.	a syrup formulation exists (Wellcome)
Dapsone **	1.5 mg/kg.	

* Used mainly by tourists. ** Not recommended if <6 weeks.

TRAVELLER'S CHEMOPROPHYLAXIS.

a)- General comments. For the purpose of malaria chemoprophylaxis, a short term visitor to an endemic area will always be considered as a traveller whether he has always been non-immune or is an immigrant who has lost his acquired immunity after living for several years in a non endemic area. The best advice will be to recommend a safe and efficient drug adapted to the geographic area of travel, with no clear counterindications for the particular traveller, and finally the importance of compliance should be stressed without which the efficacy of the drug is considerably reduced. The importance of starting before reaching the transmission zone and of the 4 weeks drug intake after returning to Europe can not be overemphasized. In this way we are able to prevent *P.falci parum* infections during the last days before departure can be prevented and any experienced traveller to Africa will be aware of the fact that many return flights from this continent are night flights where tourists spend a considerable amount of time in airports generally offering little protection against mosquitos.

This said, travellers should also be aware that there is no wonder pill giving absolute protection, simply because there is no drug that can interfere with the development of sporozoites just after they have been inoculated by the *Anopheles* mosquito.

Minor adverse reactions to chemoprophylactic drugs against malaria have been recorded by several groups of researchers, with similar rates for whatever drug or combination of drugs used^{17, 18}. Our study in Spanish travellers confirmed the above data as well as those of compliance (similar to the Chloroquine+Paludrine group). However we realized that non compliance in the Mefloquine group was due to the travellers' feeling of uneasiness when having clinical symptoms in relation with the CNS: anxiety, hyperkinesia and poor mental concentration, all experienced by patients under Mefloquine and not recorded in travellers taking the other drugs¹⁹.

b)- Geographical Areas of Drug Utilization.

The following countries have been listed after consulting sources corresponding to different groups of epidemiological surveillance based in Europe: Conseil Supérieur d'Hygiène Publique de France²⁰, the Public Health Laboratory Service (LSHTM)²¹ and the WHO official publications²². The distribution of the species can be consulted in other chapters.

Countries where Chloroquine remains the first choice.

AFRICA.- Algeria, Cape Verde, Egypt (el Fayoum), Lybia, Mauritius and Morocco.

AMERICA.- Argentina (North), Belize, Bolivia (South), Costa Rica Guatemala, Haiti, Honduras, Mexico, Nicaragua, Paraguay (East), Perú (except in the areas bordering the neighbour countries), Dominican Republic (area bordering with Haiti), El Salvador and Panamá (North).

ASIA.- Azerbaïdjan (South), Tadjikistan (South), China (North-East).

MIDDLE EAST.- Iran (except (SouthEast), Iraq (Northern areas below 1500 mt. and Basrah prov.) Syria (limited foci in the North) Turkey (Çukurova, Amikova and Anatolia).

Countries where Cl+P or Mefloquine are used as first choice.

AFRICA.- Benin, Botswana, Burkina Faso, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Madagascar, Mali, Mauritania, Namibia, Niger, Republic of South Africa (Transvaal, Natal) Senegal, Sierra Leone, Somalia, Tchad and Togo.

ASIA.- Afghanistan, Bhutan, India, Indonesia (except Irian Jaya) Malaysia (hinterland foci), Nepal, Pakistan, Philippines, Sri-Lanka.

MIDDLE EAST.- Iran (South-East), Oman, Saudi Arabia (West), United Arab Emirates, and Yemen.

Countries where Mefloquine will be the first choice*.

* Except for trips longer than 6 months.

AFRICA.- Angola, Burundi, Camerún, Central Africa Republic, Comores, Congo, Djibouti, Eritrea, Ethiopia, Equatorial Guinea, Gabon, Kenya, Malawi, Mayotte, Mozambique, Nigeria, Rwanda, Sao Tomé & Principe, Sudán, Swaziland, Tanzania, Uganda, Zaire, Zambia and Zimbabwe.

AMERICA.- Bolivia (North), Brazil (risk areas: Amazonia, Mato Grosso, Rondonia, Pará, Maranhao), Colombia Ecuador, French Guyana, Guyana, Panamá (South), Perú (East), Surinam and Venezuela.

ASIA.- Bangladesh, Cambodia, China (Yunan, Hainan) Laos Myanmar Republic, Thailand (in forest areas but not in the Cambodia and Myanmar borders), Vietnam, Malaysia (Sabah).

In any patients having contraindications for Chloroquine and/or Mefloquine, Doxycycline (100 mg/day) can be used. Doxycycline will be also the drug of choice for the bordering areas of Thailand with Cambodia and the Myanmar Republic.

The South Pacific Area. In this geographical area, Mefloquine as well as the combination Chloroquine+Pyrimethamine/DDS (Maloprim*) can be used.

The countries with endemic malaria are the following:

Indonesia (Irian Jaya), Papua New Guinea, Vanuatu.

Further to the East there are to date no other countries in the Pacific where malaria is endemic.

c)- Drugs. Their adverse reactions and counterindications.

We will now review the drugs (or combination of drugs) individually:

CHLOROQUINE. A 4-aminoquinoline which is a blood schizonticide of rapid action. Despite the widespread status of chloroquine resistance it is still widely used in tropical areas as the drug of choice in MCH clinics where chemoprophylaxis is implemented against the selected target groups. Secondary effects on the retina only occurs with prolonged use. The development of neuroretinitis is a possibility that requires more than 50 grs accumulated over several years (1 year accumulation is usually >15 grs.). However a number of american missionaries have been evaluated after more than 20 ys of accumulated chloroquine and no one case of retinitis has been diagnosed²³. The drug is also gametocytocidal against *P.vivax*, *P.ovale* and *P.malariae*.

At present the usefulness of this drug is restricted to areas of Central America and the Caribbean (Haiti, Dominican Republic) where the *P.falciparum* strains are sensitive to Chloroquine, as well as in the Middle East.

Adverse effects and Counterindications. The drug is not recommended in patients with psoriasis or with an active gastroduodenal ulcer. In both cases, a relapse of the condition is possible. There have been occasional reports in patients with a low seizure threshold therefore the drug is not recommended in patients with a past personal or family history of epilepsy²⁴.

The most frequently reported adverse effects belong to the gastrointestinal tract: abdominal pain, vomiting, nausea. Corneal crystal deposition without affecting the vision is frequently seen in residents after few months of taking the drug.

PROGUANIL. A slow acting schizonticide used only as a prophylactic drug. As safe in pregnancy as chloroquine but a folic acid supplement must be added.

Adverse Effects and Counterindications. This is the safest of all chemoprophylactic drugs, with practically no counterindications. Minor gastrointestinal problems like heartburn or epigastric pain have been reported mainly by people who take the drug while fasting. Mouth ulcers are definitely the more disturbing of the adverse effects reported.

CHLOROQUINE+PROGUANIL 4-aminoquinoline and a biguanide or type 2 antifolate that can inhibit any stage of the malaria parasite. This combination is still a first choice in a number of West African countries according to our English and French sources as well as in areas of Mefloquine choice when this drug is to be administered for long periods.

Adverse effects and contraindications. The same as for both drugs taken individually. Mouth ulcers disappear after reducing the usual dose from 200 mgs to 100 mgs without reducing the expected protection against the infection.

D.D.S.+ PYRIMETHAMINE A sulphone which is a type 1 antifolate with a slow schizontocidal action is associated here with a type 2 antifolate. First recommended for malarial areas of the South Pacific and Indonesia it has now extended its geographical action to areas where both Chloroquine

and Mefloquine resistance coexist. Having been found safe as prophylaxis in Gambian children, it is now used in other areas of Africa for the same purpose.

Adverse effects and Contraindications. When the weekly dosage was doubled at two tablets per week, cases of potentially fatal agranulocytosis have been reported (REF). Persons with hereditary NADH methaemoglobin reductase deficit can develop clinical methaemoglobinemia.

People with known susceptibility to sulphonamides compounds can not take the drug as Dapsone (D.D.S) could induce potentially fatal reactions of the dermato-exfoliative type. Sporadic severe cases could even be accepted depending on the severity of the malaria situation as a whole. The drug has been used extensively in infants and children of the subsaharan zone, and no serious side effects have been reported²⁵.

MEFLOQUINE. An arylaminoalcohol (quinoline methanol) is a blood schizontocide for all species of malaria parasites. Despite his relatively recent emergence its indiscriminated utilization is causing a rapid dissemination of resistance to this drug. This is particularly true for the area of the Thailand/Cambodian frontier and it is feared that the same phenomenon will soon occur in other tropical areas. The sole advantage of this dissarray is that Chloroquine sensitivity is recovering in the areas where it has not been used for some time²⁶. French authors have shown Mefloquine resistance in some areas of West Africa where the drug has not been used yet²⁷

Adverse effects and contraindications. The drug is not indicated in patients with personal or family history of epilepsy, patients under hypnotic and antidepressant drugs as well as in persons with cardiac arrhythmias.

The prevalence of adverse effects is similar as with other drugs according to several studies. This, together with the easiness of the regimen and its efficacy²⁸ were determinant for the widespread use of this drug. Compliance should be easier with Mefloquine that has to be taken only once a week, however the frequently reported CNS symptoms (insomnia, vertigo, hyperkinesia etc) often leads to the patient's discontinuation of the treatment. The risk for developing acute psychotic reactions under chemoprophylactic regimes has been evaluated at 1/12000 persons²⁹. A case of Mefloquine induced grand mal seizure in a non epileptic patient has been recently described³⁰.

Cases of *P.falciparum* infections in Dutch short time visitors to the tropics under Mefloquine prophylaxis indicate that the drug should be started earlier than usually prescribed or a loading dose should be given instead, if adequate protecting circulating levels of the drug are to be achieved³¹. At present there is no consensus concerning the length of time in which the drug should be used. Not more than 4 to 6 months according to most European authors and several years according to US publications.

DOXYCICLINE. Antibiotic with slow marked actions at the blood stage of the parasites. Recommended in areas of multiple drug resistance such as the Thailand/Cambodia or the Thailand/Myanmar borders especially for short term travellers. The drug can also be recommended in patients with clear contraindications for Mefloquine use when that was the drug of choice. As with other tetracyclines, doxycycline should not be used in children nor in pregnant or lactating women.

Adverse effects and contraindications. Some have been already mentioned. Vaginal candidiasis, oesophageal ulcers and intestinal flora modifications are some of the problems inherent to the administration of this drug together with the well known photosensitivity reactions. To what extent its prolonged administration could interfere with oral contraceptive medication is still unknown.

Finally it should be remembered that nowadays none of the regimens described above is one hundred per cent effective in suppressing a *Plasmodium* infection; however their important role in reducing morbidity and mortality when used both as a control tool or in travel medicine cannot be denied. Another important point is the demonstration that for each drug regimen, compliance with the prophylaxis strongly influenced the degree of protection achieved³²

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