Malaria and the traveller

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Key words: Malaria, *Plasmodium falciparum*, traveller, chemoprophylaxis, insect bite avoidance

Malaria has reached epidemic proportions. About 40% of the world's population live in malarious areas. It is estimated that 400 million people are infected by malaria each year and of these, 1-3 million die, mostly children under five years of age.[1] In the year 2000, malaria was estimated to be the cause for the loss of nearly 45 million Disability Adjusted Life Years (DALYs) and this accounts for 13% of all DALYs associated with infectious diseases.[2] Malaria has gained importance in Western Europe, including Malta, mainly due to the increasing tourism to malaria endemic countries. There have been 21 reported cases of malaria in Malta between the years 2000-2003.[3]

Life cycle of malaria parasite

There are two phases in the malaria life cycle (Figure 1); one occurring in the intermediate host (humans, birds, reptiles) and the other occurring in the definitive host (mosquitoes). This review will concentrate mainly on the intermediate host.

When an infected anophele mosquito bites a human being, sporozoites are inoculated into the subcutaneous tissue, or rarely, into the bloodstream. These are then taken up by hepatocytes through a receptor-mediated mechanism.[4] Here, the sporozoites develop into schizonts and depending on the infecting plasmodium species, will either divide into a large number of merozoites or enter into a dormant phase, hypnozoites, the latter occurring with infection by *Plasmodium ovale* and *vivax*. Once merozoites are released into the circulation, they invade erythrocytes and become ring-shaped trophozoites.[5] Trophozoites enlarge by feeding on haemoglobin and the by-product of digestion is released within the red blood cell as insoluble haemozoin. When the trophozoite has become mature, it forms a schizont and starts to divide so that by the end of the cycle, there would be between 8-24 merozoites ready to emerge and infect new red cells. This cycle is known as erythrocytic schizogony. Eventually some of the merozoites will differentiate into immature gametocytes. These are important for continuation of the life cycle within the definitive host. Once immature gametocytes are taken up by the mosquito during a blood meal, they differentiate into macrogametes and microgametes within the stomach. After a process of exflagellation, the microgamete releases 6-8 flagella, one of which goes on to fertilise the macrogamete. Within 24 hours the resulting zygote develops into an ookinete and this penetrates the midgut wall to become an oocyst lying between the midgut epithelium and basal lamina.[6] Following a series of asexual divisions, a number of sporozoites are formed. These are then released from the oocyst and migrate towards the salivary glands ready to be transferred during the mosquito's next blood meal.

Classification and mode of action of antimalarials

Antimalarials may be classified depending upon the stage of the malaria cycle they act upon. This in turn will determine their use. (Figure 1, Table 1)

A. Tissue schizontocides – defined as compounds acting on pre-erythrocytic forms in the liver. This may in turn be divided into:

Tissue schizontocides used for causal prophylaxis. These agents prevent development of the parasite within the liver. Thus, merozoites are not released into the bloodstream and both the asexual and sexual stages of the lifecycle are prevented. Example include pyrimethamine.[7,8]

Tissue schizontocides used to prevent relapse. These kill the dormant hypnozoites in the liver that are responsible for relapses seen with *P. vivax* and *P. ovale* infections. Example includes primaquine.[7,8,9]

Figure 1: Action of antimalarial drugs at different stages in the life cycle of Malaria parasite in the Anopheles mosquito and human hosts

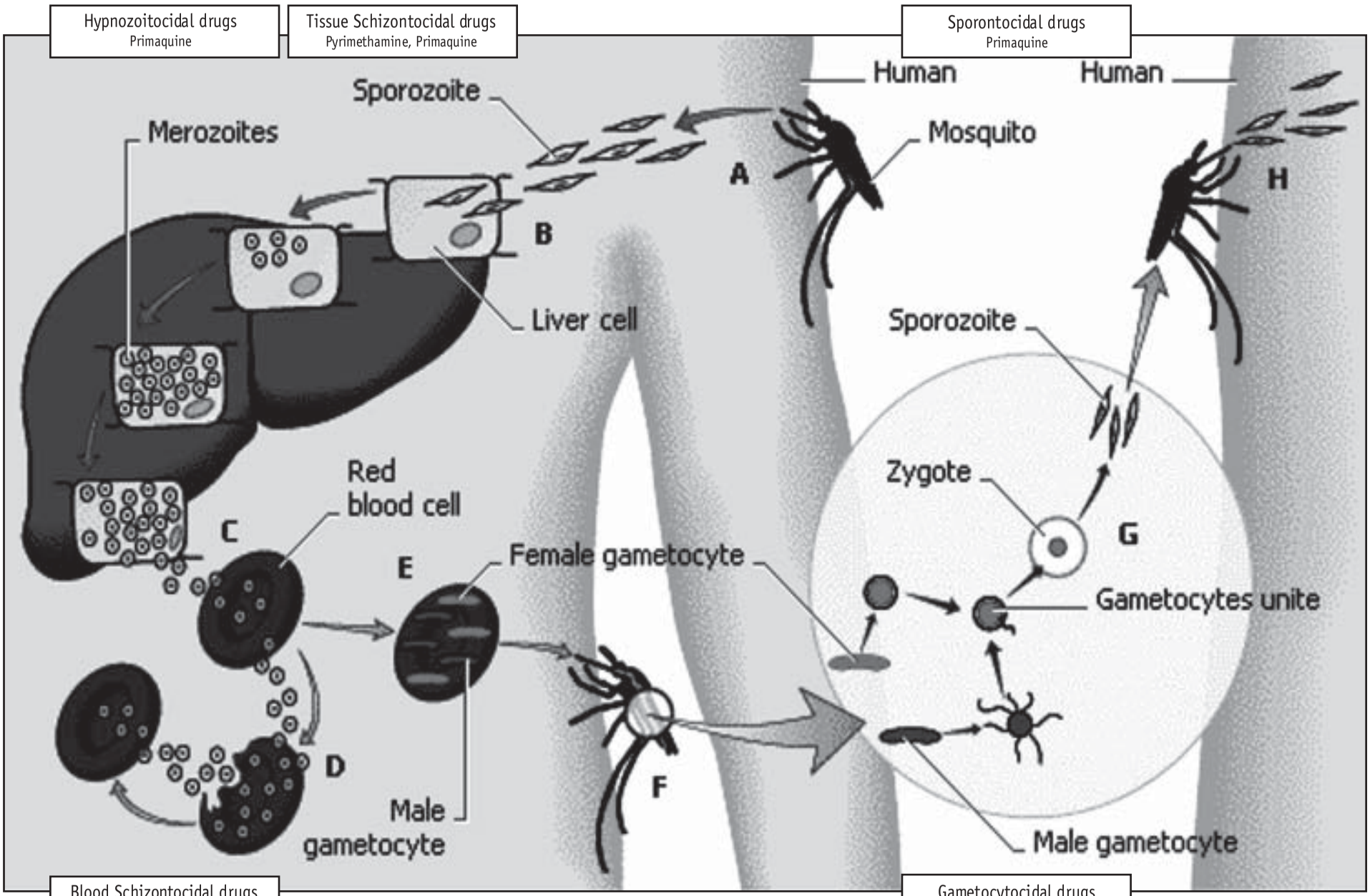

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Table 1: Mode of action and use of antimalarials

Drug Class	Classification	Mode of action	Use
Arylaminoalcohols Quinine Quinidine Mefloquine Halofantrine	Blood schizontocides	Precise mode of action is still not clear. Believed to act by inhibiting the polymerisation of haemin into haemozoin[12]	• Treatment of acute disease – quinine is the drug of choice. Due to its increased cardiotoxicity, quinidine is used only if quinine is not available[7] • Suppressive prophylaxis – mefloquine is used in areas of chloroquine-resistant malaria
4 – aminoquinolines and related compounds Chloroquine Amodiaquine Mepacrine Pyronaridine	Blood schizontocides	Precise mode of action still not clear. Believed to act by inhibiting the polymerisation of haemin into haemozoin. Also appears to affect cell growth by interfering with DNA[12,13]	• Treatment of non-falciparum malaria - should not be used in falciparum, unknown infective species or mixed infection[14] • Suppressive prophylaxis – Chloroquine • Amodiaquine, Mepacrine and Pyronaridine – use obsolete and not recommended[7]
Sulfones and sulfonamides[a] Dapsone Sulfamethoxypyrazine Sulfadoxine	Type I antifolate inhibitors	Compete for dihydropteroate synthase found only in the malaria parasite and required in the pathway to synthesize DNA[7,8]	• Causal prophylaxis • Treatment
Biguanides and diaminopyrimidines Proguanil Chlorproguanil Pyrimethamine[a]	Type II antifolate inhibitors	Inhibit dihydrofolate reductase used by the malaria parasites to make folinic acid cofactors for synthesis of DNA. Prevent the completion of schizogony leading to large abnormal looking trophozites[11]	• Causal prophylaxis • Treatment of infections resistant to other blood schizontocides[7] • Used in combination with quinine to ensure clinical cure in quinine-resistant falciparum malaria[7] • Pyrimethamine should only be used in combination[14]
8 – aminoquinolines Primaquine	Hypnozoiticidal and gametocytocidal	Converted to quinone active metabolites in liver and are particularly active against non-growing stages of the parasite[7]	• Prevention of transmission of falciparum • Antirelapse for vivax and ovale malaria
Antibiotics Doxycycline Clindamycin Fluoroquinolones	Blood schizontocides	Inhibitors of parasitic ribosomal protein synthesis. Azithromycin is under investigation for antimalarial activity [7,12]	• Treatment: used in combination with quinine in effecting cure[7,14] • Doxycycline: a suppressive prophylactic for multiresistant falciparum malaria[14]
Peroxide antimalarials Artemisinin (from the Chinese medicinal plant *Artemisia annua*)	Blood schizontocides	Act on malaria parasite engaged in digesting haemoglobin in erythrocytes where they are thought to interfere with the conversion of haem to the nontoxic haemozin[7,15]	• Acute uncomplicated falciparum including parasites resistant to chloroquine and quinine[14]
Hydroxynaphthoquinones Atovaquone	Blood schizontocides	Atovaquone acts on the electron transport chain in the malarial mitochondrion causing collapse of the mitochondrial membrane potential. Proguanil potentiates this[16,17]	• Atovaquone (250mg) with proguanil (100mg) combination (Malarone™) indicated for prophylaxis and treatment particularly where drug-resistant falciparum malaria exists[16]

a In most cases Type I antifolate drugs are combined with Type II antifolate drugs for synergistic action. Combinations include: dapsone with pyrimethamine (Maloprim™, Deltaprim™), sulfamethoxyprazine with pyrimethamine (Metakelfin™), sulfadoxine with pyrimethamine (Fansidar™)

B. Blood schizontocides – these act on the asexual erythrocytic part of the malaria life cycle. They act in one of two ways. Drugs, such as mefloquine and quinine, concentrate in the parasite lysosomes within the infected erthyrocytes, thus interfering with the parasitic digestion of haemoglobin. The breakdown product, haemin, is toxic to the parasite and is normally polymerised into non-toxic haemozoin, an action inhibited by the drugs. Sulfones and proguanil have antifolate activity, thereby inhibiting different stages of DNA production in the parasite. [7,8,10,11]

C. Gametocytocides – these include primaquine and destroy the sexual forms of the parasite in the blood, hence preventing transmission to the mosquito.[7,8,9]

D. Sporontocides – these prevent parasite transmission by preventing oocyte formation within the mosquito stomach wall. Sporozoite formation is therefore inhibited and this prevents parasite transmission to the human host. Primaquine exhibits this mode of action.[7,8]

Use of antimalarial combinations

Multidrug resistance is the biggest challenge hindering effective prophylaxis and treatment and has made it necessary to use antimalarial combinations. Combination therapy has been defined by the World Health Organization (WHO) as "*the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination*".[18] Drugs used in combination are usually blood schizontocidal drugs that have different modes of action on the parasite. Various factors contribute towards making an ideal combination. These include: safety (synergistic and additive adverse effects may be a problem when drugs are used in combination), acceptability to the patient (side effect profile, product presentation, co-formulation in a single formulation, packaging ensuring stability in hotter climates, simple dose schedules) and potential to delay or prevent resistance development.[18,19] Limitations to use of combination therapy include: cost (with combinations costing up to 10 times that of monotherapy), lack of evidence in particular patient groups, such as pregnancy and paediatrics and the choice of drug combinations depending on the resistance patterns.[18]

Malaria and the traveller

The UK Guidelines for travellers define the aim of prophylaxis as *'to prevent illness and death in people who travel to areas where malaria is transmitted.'*[20] The risk of acquiring malaria can be reduced by providing adequate and evidence-based advice to travellers and appropriate chemoprophylactic cover when needed. It is very common for travellers preparing to go abroad to present at community pharmacies for insect bite repellents and over-the-counter medications to take on their journey abroad. To ensure successful malaria prophylaxis, the pharmacist requires a sound knowledge of four key steps: **A**wareness, **B**ites, **C**ompliance and **D**iagnosis.[20]

Awareness – knowing about the risk of malaria

In choosing the most effective regimen and ensuring that appropriate advice is given, various factors affecting the risk of malaria need to be considered for each individual. These include:

- **Places to be visited**
  Malaria is only present in particular areas of the world and is endemic and easily transmissible in areas lying between 64° North and 32° South.[21] Within this region, risk of transmission may be higher in one area compared to another; for example, in parts of Tanzania, malaria is holoendemic and transmission occurs perennially while in Sudan, malaria is mesoendemic and transmission is seasonal.[22] The difference lies in the entomological inoculation rate, which is the average number of infective bites per unit time. This varies in different areas and can range from less than 1 to more than 1000 infected bites per year in different parts of Africa.[23]
- **Areas of drug resistance**
  The presence of chloroquine-resistant falciparum malaria is increasing worldwide with only small areas of the world still having chloroquine-sensitive *Plasmodium falciparum;* for example, the Caribbean regions.[20]
- **Duration of visit**
  The duration of stay in a malarious area is important. It is known that the longer one spends in a malarious region the higher the risk of acquiring malaria.[20] In fact, with short visits to certain areas of Africa, the use of chemoprophylaxis is questionable since the risks of adverse events with these medications may outweigh the risks of acquiring the disease.[12] In such cases, expert advice needs to be sought.
- **Type of traveller and degree of exposure**
  This includes pattern of activity at dusk/dawn and mode of travel. Backpackers and travellers working in rural areas are at higher risk. Likewise those visiting friends and relatives may be at a higher risk due to the often misconceived idea that since they frequently visit the malarious areas they are immune to the disease.[12,20]

Bites – learning how to prevent or avoid mosquito bites

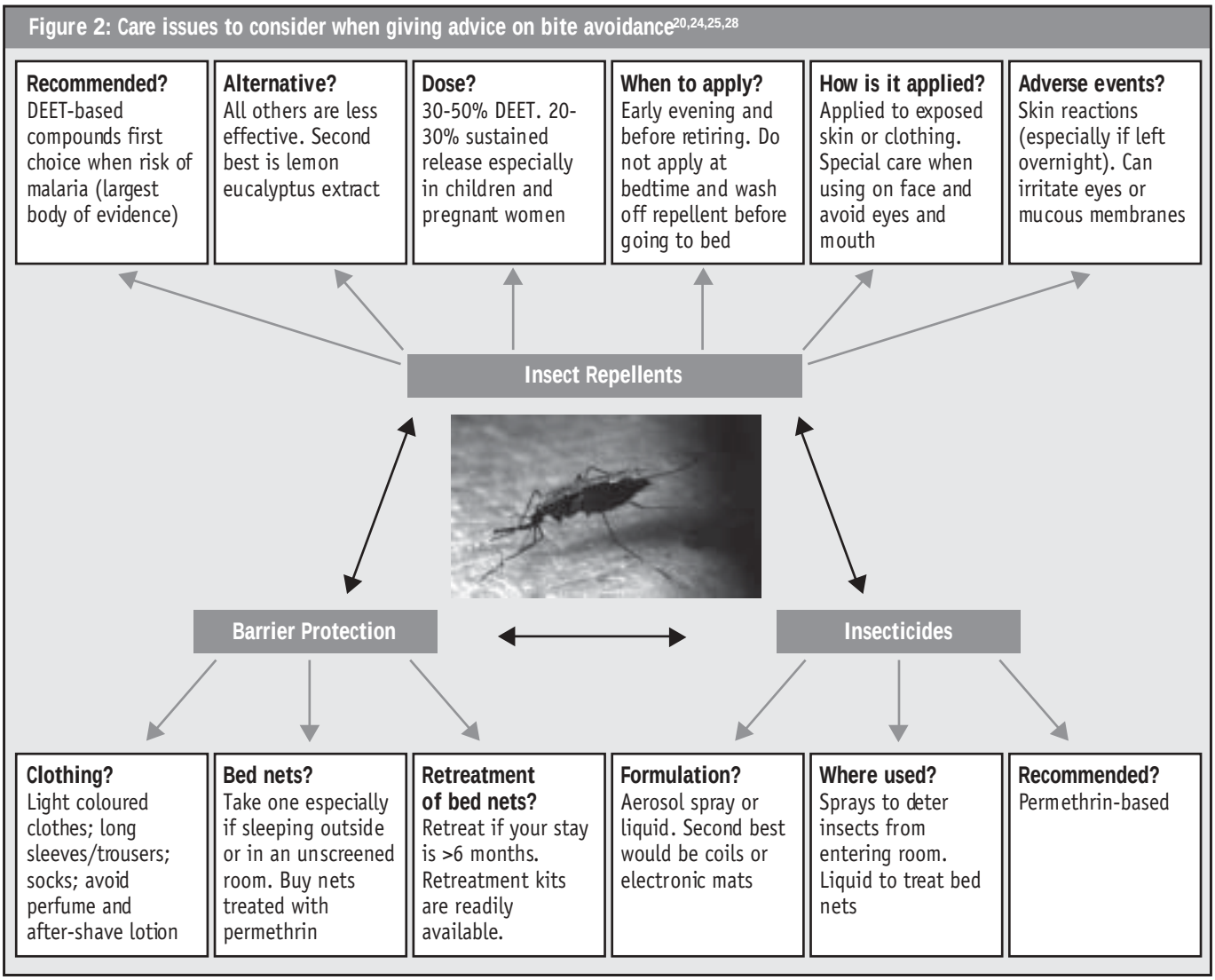
Travellers need to be advised on precautions to prevent insect bites (Figure 2). Since insect repellents are the mainstay of bite avoidance, the pharmacist should have a sound knowledge to ensure effective use. Repellents need to be applied frequently since their duration of activity is diminished by sweat on the skin, the ambient and body temperatures, windy conditions and activities such as swimming.[24,25] Travellers should therefore be advised to reapply more frequently than the time stated on the label if the effects seem to be wearing off.[24] Repellents are also not suitable for overnight protection and insecticide-impregnated mosquito nets are therefore crucial unless an air-conditioned room with sealed windows is used.[25] When a sunscreen is needed, this

should be applied first and the repellent applied over.[24] Sunscreens may lose some of their efficacy and therefore other additional precautions should be taken.[26,27] It is worth noting that research has indicated that travellers are more likely to comply with chemoprophylaxis rather than use of repellents and consequently the pharmacist needs to select a product that is acceptable to the patient to maximise concordance.[24] DEET remains the 'gold standard' and an independent trial comparing this to other repellents showed DEET to be the most effective.[24] Unfortunately, DEET-containing products are not always readily available due to controversy about adverse effects. Due to the length of time it has been on the market, the largest amount of evidence is available for DEET and analysis indicates a remarkable safety profile.[27,28] In fact, guidelines formulated by expert panels still recommend it as the first choice where there is a risk of malaria.[20] Patients should be warned that DEET may damage plastic objects and synthetic fabrics.[25] Pharmacists should also note that there is little or no evidence to support the use of electronic devices that claim to repel mosquitoes by emitting an ultrasonic noise.[20,24]

Compliance with appropriate chemoprophylaxis

It is crucial to refer to suitable updated sources (examples of suitable sources are listed at the end). One should keep in mind that different drugs are available in different countries and guidelines may therefore vary leading to confusion. It is recommended to start treatment one week before to enable any adverse effects to be detected beforehand and to ensure that the blood level of the drug is within therapeutic range prior to reaching the malaria endemic region.[12,14,20] Mefloquine is an exception and current guidance recommends starting the drug two and a half weeks before travel ensuring that 3 doses are taken before travel and any adverse effects noted.[10,12,14,20] Atovaquone/proguanil prophylaxis should be started 24 to 48 hours before departure.[14,16] All regimens should be taken regularly during the travel period and for up to four weeks (one week in the case of atovaquone/proguanil) after return in case there is any parasite emerging from the pre-erythrocytic stage.[12,14,16,20] Drugs may be taken after meals with water to minimise adverse effects. It is worth noting that the rate of malaria contraction due to non-compliance is probably as high as that due to malaria resistance, and concordance with the prescribed regimen needs to be reinforced by the pharmacist.[12] Travellers should be advised to take enough tablets to cover

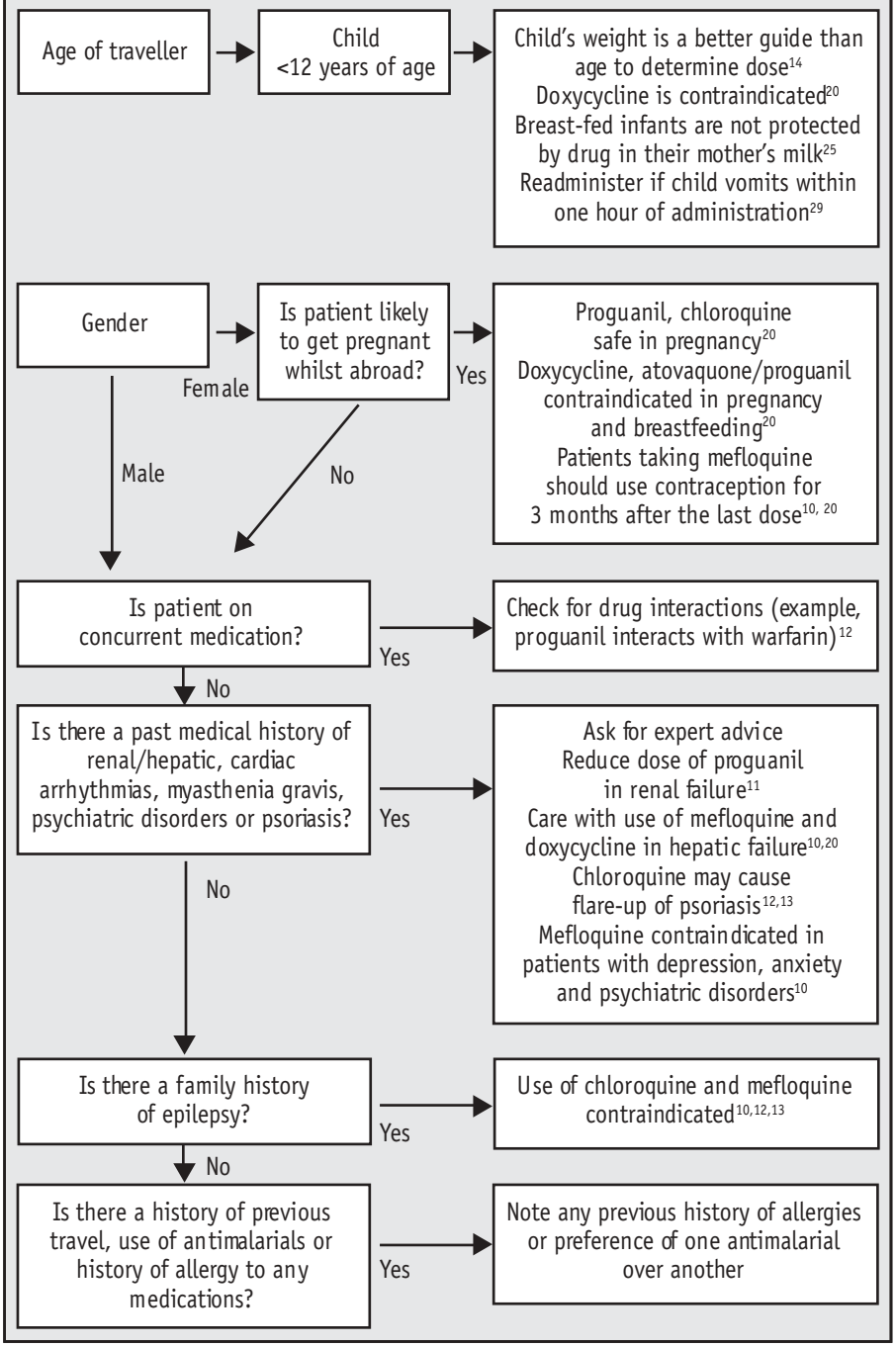
Figure 2: Care issues to consider when giving advice on bite avoidance[20,24,25,28]



the whole trip since it may be a problem to obtain these in the visiting country.[25] To ensure the most effective and least toxic chemoprophylactic for the individual patient, a number of care issues need to be considered (Figure 3) since numerous factors may complicate the choice of treatment. The incidence of adverse effects is very difficult to predict and is sometimes based on subjectivity. Though databases for reporting adverse effects are available, it is difficult to determine the exact incidence of adverse effects when drugs are used as antimalarials, since many are also used for other conditions, often at higher doses and for longer periods of time.[20] This is further compounded by the fact that increasing parasite resistance is leading to the use of newer drugs where there is less experience with respect to adverse effects.

Long-term travellers (>6 months) may pose a particular challenge since most chemoprophylactic agents are only licensed for a limited period. The following options may be considered: switching from one drug to another when the limit is reached; using proguanil with chloroquine despite the fact that resistance has been reported (may be used for periods up to 5 years[14]); not using chemoprophylaxis and seeking advice if a malaria attack occurs, or continuing beyond the licensed duration of the drug. The latter is considered the more suitable since most adverse effects occur at the start of treatment rather than later.[20]

Figure 3 : Care issues to consider when choosing appropriate antimalarial prophylaxis



Diagnosing breakthrough malaria swiftly and obtaining proper treatment

Emergency standby treatment is recommended for travellers taking prophylaxis and, who are unlikely to be within 24 hours reach of a doctor. The drug given should be different to the chemoprophylactic drug. Atovaquone/proguanil or co-artemether (artemisinin with lumefantrine) are recommended as stand-by treatment, with quinine recommended only in pregnancy.[20] Travellers should be advised to seek medical advice if they develop a febrile illness within 3 months of return.

Conclusion

Since the discovery of the malaria parasites in human blood by Charles Louis Alphonse Laveran in 1880 and the description of the complete life cycle in birds by Ronald Ross in 1898, there have been numerous breakthroughs in elucidating the pathogenesis as well as the treatment of this deadly disease.[30,31] No sooner had any hopes of malaria eradication been put forward that the first drawbacks were seen. Resistance to the most common antimalarials has necessitated looking at other alternatives, including combination treatment, in order to curb this disease.[18] Still, statistics about malaria infections worldwide are far from comforting. The "prevention is better than cure" adage definitely applies and in fact, advice and appropriate chemoprophylaxis to people travelling to malarious areas is as important as diagnosing and treating malaria cases. Table 2 lists sources of regularly updated information on the choice of appropriate antimalarials.

Practice Points

- There has been an increase in the number of malaria cases in developed countries due to an increase in tourism to endemic countries
- To ensure successful malaria prophylaxis, the pharmacist needs to ensure that the prospective traveller knows about the risk of malaria, how to avoid insect bites, comply with chemoprophylaxis and diagnose breakthrough malaria
- The choice of antimalarials to be used depend on the place to be visited, resistance patterns of malaria in the area, interactions with other medications, drug allergies and other contraindications
- Avoidance of insect bites involves the use of insect repellents, insecticides and barrier mechanisms
- Seek expert advice if the traveller is a child, pregnant woman, currently on drugs which may interact with antimalarials and co-morbidities which affect the pharmacokinetics and pharmacodynamics of the chemoprophylaxis to be used.

Table 2: Sources of regularly updated information on the choice of appropriate antimalarials

1. *British National Formulary* (guidelines based on Health Protection Agency recommendations). Available at http://www.bnf.org
2. *Travax* (site developed by NHS Scotland). Available at http://www.travax.scot.nhs.uk
3. *WHO international travel and health* (updated weekly by Weekly Epidemiological Record). Available at http://www.who.int/ith
4. *The Yellow Book* (health information for international travel). Available at http://www.cdc.org
5. *The International Society of Travel Medicine*. Available at http://www.istm.org

References

1. Marshall E. Malaria. A renewed assault on an old and deadly foe. Science 2000;290(5491):428-430
2. WHO World Health Report 2000, Geneva: WHO, 2000
3. Disease Surveillance Unit, Department of Public Health, Malta. Available at URL: http://www.health.gov.mt/dsu/reports/index.htm Accessed on 1st November 2004
4. Miller LH, Baruch DI, Marsh K, Doumbo OK. The pathogenic basis of malaria. Nature 2002;415(6872):673-79
5. Bannister LH, Hopkins JM, Fowler RE, Krishna S, Mitchell GH. A brief illustrated guide to the ultrastructure of Plasmodium falciparum asexual blood stages. Parasitology Today 2000;16(10): 427-33
6. Billingsley PF, Sinden RE. Determinants of malaria-mosquito specificity. Parasitology Today 1997;13(8):297-301
7. Warrell DA. Treatment and prevention of malaria. In Bruce-Chwatt's Essential Malariology. Edited by HM Gilles and DA Warrell. 3rd edition. London: Arnold Publishers; 1993.
8. Tracy JW, Webster LT Jr. Drugs Used in the Chemotherapy of Protozoal Infections: Malaria. In: Goodman and Gilman's The Pharmacological Basis of Therapeutics. Edited by Hardman JG, Limbird LE and Goodman Gilman A. 10th Edition. New York: Mc Graw Hill Companies, Inc.; 2001
9. Drug Information: Primaquine. Available at URL: www.mdbrowse.com/Druginf/P/Primaquine.htm Accessed on 29th September 2004
10. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Lariam. 2003. Available at url: www.medicines.org.uk. Accessed on: 24th September 2004
11. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Paludrine. 2001. Available at url: www.medicines.org.uk. Accessed on 28th September 2004
12. Goodyer L. Travel Medicine (4): Malaria. Pharm J 2000;264:405–10
13. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Nivaquine. 2003. Available at url: www.medicines.org.uk. Accessed on 24th September 2004
14. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary (Vol 48, September 2004). Available at URL: www.bnf.org
15. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Riamet 2002. Available at url: www.medicines.org.uk. Accessed on 5th October 2004
16. Electronic Medicines Compendium for the Professional. Specific Product Characteristics. Malarone 2002 Available at url: www.medicines.org.uk. Accessed on 1st October 2004
17. Nosten F. Prophylactic effect of Malarone against malaria: all good news? Lancet 2000;356:1864-65
18. Antimalarial Drug Combination Therapy. Report of a WHO Technical consultation. April 2001.
19. Kremsner PG, Krishna S. Antimalarial combinations Lancet 2004; 364:285-94.
20. Bradley DJ, Bannister B on behalf of the Health Protection Agency Advisory Committee on Malaria Prevention for UK travellers. Guidelines for malaria prevention in travellers from the United Kingdom for 2003. Commun Dis Public Health 2003:6(3):180 – 99
21. Gilles HM. Epidemiology of malaria. In Bruce-Chwatt's Essential Malariology. Edited by HM Gilles and DA Warrell. 3rd edition. London. Arnold Publishers 1993
22. Babiker HA, Lines J, Hill WG, Walliker D. Population structure of Plasmodium falciparum in villages with different malaria endemicity in east Africa. Am J Trop Med Hyg 1997;56(2):141-7
23. Beier JC, Killeen GF, Githure JI. Short report: Entomologic inoculation rates and Plasmodium falciparum malaria prevalence in Africa. Am J Trop Med Hyg 1999;61(1):109-113
24. Goodyer L. Travel medicine (6): Bite avoidance. Pharm J 2000;265:298-304
25. International Association for Medical Assistance to Travellers. How to protect yourself against malaria. 2004 ed. Available at url: www.iamat.org
26. Montemarano AD, Gupta RK, Burge JR, Klein K. Insect repellents and the efficacy of sunscreens. Lancet 1997;349:1670-71
27. Fradin MS. Mosquitoes and mosquito repellents: a clinician's guide. Ann Intern Med 1998;128:931-40
28. Goodyer L, Behrens RH. Short report: the safety and toxicity of insect repellents. Am J Trop Med Hyg 1998;59(2):323-24
29. Goodyer L. Childhood malaria – prevention and emergency self-treatment. Pharm J 2002;269:787-88
30. Dobson MJ. The malariology centenary. Parassitologia 1999;41:21-32
31. Hay SI, Guerra CA, Tatem AJ, Noor AM, Snow RW. The global distribution and population at risk of malaria: past, present, and future. Lancet Infect Dis 2004;4:327-36