REVIEW ARTICLE

Drug Safety 2004; 27 (1): 25-61
0114-5916/04/0001-0025/$31.00/0

Antimalarial Drug Toxicity
A Review

W. Robert J. Taylor[1,2] and *Nicholas J. White*[3,4]

1 WHO/Tropical Disease Research (TDR), Geneva, Switzerland
2 Centre for Infectious Diseases, Royal Free and University College Medical School, Windeyer Institute of Medical Sciences, London, United Kingdom
3 Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
4 Centre for Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom

Contents

Abstract

Malaria, caused mostly by *Plasmodium falciparum* and *P. vivax*, remains one of the most important infectious diseases in the world. Antimalarial drug toxicity is one side of the risk-benefit equation and is viewed differently depending upon whether the clinical indication for drug administration is malaria treatment or prophylaxis. Drug toxicity must be acceptable to patients and cause less harm than the disease itself. Research that leads to drug registration tends to omit two important groups who are particularly vulnerable to malaria – very young children

and pregnant women. Prescribing in pregnancy is a particular problem for clinicians because the risk-benefit ratio is often very unclear.

The number of antimalarial drugs in use is very small. Despite its decreasing efficacy against *P. falciparum*, chloroquine continues to be used widely because of its low cost and good tolerability. It remains the drug of first choice for treating *P. vivax* malaria. Pruritus is a common adverse effect in African patients. As prophylaxis, chloroquine is usually combined with proguanil. This combination has good overall tolerability but mouth ulcers and gastrointestinal upset are more common than with other prophylactic regimens. Sulfadoxine/pyrimethamine is well tolerated as treatment and when used as intermittent preventive treatment in pregnant African women. Sulfadoxine/pyrimethamine is no longer used as prophylaxis because it may cause toxic epidermal necrolysis and Stevens Johnson syndrome. Mefloquine remains a valuable drug for prophylaxis and treatment. Tolerability is acceptable to most patients and travellers despite the impression given by the lay press. Dose-related serious neuropsychiatric toxicity can occur; mefloquine is contraindicated in individuals with a history of epilepsy or psychiatric disease. Quinine is the mainstay for treating severe malaria in many countries. Cardiovascular or CNS toxicity is rare, but hypoglycaemia may be problematic and blood glucose levels should be monitored. Halofantrine is unsuitable for widespread use because of its potential for cardiotoxicity.

There is renewed interest in two old drugs, primaquine and amodiaquine. Primaquine is being developed as prophylaxis, and amodiaquine, which was withdrawn from prophylactic use because of neutropenia and hepatitis, is a potentially good partner drug for artesunate against falciparum malaria. Atovaquone/proguanil is a new antimalarial combination with good efficacy and tolerability as prophylaxis and treatment. The most important class of drugs that could have a major impact on malaria control is the artemisinin derivatives. They have remarkable efficacy and an excellent safety record. They have no identifiable dose-related adverse effects in humans and only very rarely produce allergic reactions. Combining an artemisinin derivative with another efficacious antimalarial drug is increasingly being viewed as the optimal therapeutic strategy for malaria.

The estimated annual, global malaria burden is 300–500 million cases.[1] *Plasmodium falciparum* is the predominant species and, together with *P. vivax,* accounts for most of the world's malaria. Approximately 1.5–2.7 million deaths occur annually, mostly in African children with *P. falciparum*, the form of malaria that causes severe and complicated disease.[2]

Clinicians in the tropics and temperate zones may view malaria from different perspectives, especially regarding the risk-benefit ratio. Malaria is a common infection in endemic countries where it causes considerable morbidity, and is uncommon in temperate zones where it generally falls into the differential diagnosis of an imported fever. The physician based in the temperate zone is orientated more towards malaria prevention than treatment and may be unfamiliar with the clinical assessment of malaria. Cost and access to treatment often limit therapeutic choices in the tropics; these limitations do not generally apply in temperate zones. Drug-related toxicity and its risk must be balanced against the likely outcome of malaria treatment or prophylaxis and the circumstances of clinical practice. In this regard, there are no contraindications to prescribing an effective drug that will save a life.

Assessing the risk-benefit ratio is not primarily the task of busy clinicians, who rely on recommendations by national or international authorities that have reviewed all the pertinent research data. Never-

theless, clinicians should have an appreciation of how these guidelines are produced and of the quality of the research data that has been evaluated. Randomised, controlled trials are the best way to gather evidence on the effectiveness of a health intervention.[3] Open-label trials are subject to investigator bias especially regarding adverse events and their relationship to the study drugs used. Retrospective studies generally use questionnaires or telephone interviews. Although subject to recall bias of the interviewees, they still provide good quality evidence. Case reports are difficult to evaluate but may serve as a warning of possible serious or rare drug-related toxicity.

Assessing 'adverse drug reactions', 'adverse events', 'drug-related toxicity', 'side effects', or 'treatment-emergent symptoms and signs' is difficult. Standard definitions should be used.[4] Estimating the risk of drug toxicity is also important but no standard system exists to quantify and describe risk. In addition, acute malaria is associated with malaise, fever, nausea, vomiting, abdominal pain, anaemia, and sometimes diarrhoea – all of which could be iatrogenic. These symptoms are commonly mentioned in reports as being possible drug-related adverse effects, even though they resolve coincident with recovery from the infection and are therefore in all probability malaria related.

One area of potential confusion for clinicians is when a drug is 'absolutely' or 'relatively' contraindicated, 'unsuitable', or 'can be used with caution'. Different recommendations by different authorities compound the confusion. Difficulties arise when data are insufficient, leaving much room for interpretation. This is a particular challenge when prescribing for pregnant women. By contrast, adequate data allow for recommendations to be made with confidence. The clinical indication for the drug is also a key consideration. A physician who is faced with a sick, non-immune patient will be more willing to prescribe a more effective but, possibly more toxic, drug whereas the same physician will be more guarded if prescribing the same drug for malaria prophylaxis, especially if there might be a relative contraindication to using that drug.

Pregnant women with malaria are a group for whom the risk-benefit ratio is often unclear. Consequently, clinicians are wary of prescribing in pregnancy. Reluctance by drug manufacturers to test drugs in pregnant women is well known. As a result, data in pregnancy often become available because of accidental exposure or because public health necessity leads to the use of drugs. Malaria in pregnancy poses a significant risk to mother and fetus because of high maternal and fetal morbidity and mortality.[5,6]

Antimalarial drug resistance is now a global challenge that compromises drug efficacy. *P. falciparum* is resistant to virtually all of the standard antimalarial drugs and chloroquine-resistant *P. vivax* is emerging.[7] Recommending optimal treatment or prophylaxis becomes more challenging. Patient compliance is another important determinant of drug effectiveness and may be compromised if drug toxicity is unacceptable.[8]

Drug treatment policy in most malaria-endemic countries centres on the use of single agents used in sequence once the first-line drug line is failing. This policy will become unsustainable because of the limited number of affordable antimalarial drugs, and the small number of drugs in development. A new therapeutic strategy has been proposed recently, namely, combining standard or new antimalarial drugs with an artemisinin derivative with the aim of increasing drug efficacy, reducing transmission, and retarding the development of resistance.[9] This approach has a similar rationale to the use of multiple drugs in the treatment of tuberculosis and HIV infection. It has two major implications. Firstly, for drug-related toxicity, will two drugs be more toxic than one? Secondly, older drugs whose efficacy has been eroded by resistance may be given a new lease of life.

This article will review the adverse effects of the widely used antimalarial drugs, the artemisinin derivatives, and other newly introduced drugs.

1. Method and Search Strategy

We used a Medline search (from 1965 to May 2003) by using various combinations of the following key words: malaria, drug toxicity, toxicity, side effects, adverse effects, tolerability, the name of the individual antimalarial drugs: quinine, chloroquine, sulfadoxine/pyrimethamine, primaquine, atovaquone/proguanil, amodiaquine, artesunate,

artemether, and specific clinical diagnoses, e.g. hepatitis, rash, toxic erythema, erythema multiforme.

Articles pre-dating Medline were sought from published papers. We wrote to recognised experts to answer specific queries; their responses have been cited in the text. The British National Formulary and WHO publications were used to gain a national and international perspective on prescribing recommendations.

2. Chloroquine

Chloroquine has been the standard antimalarial drug for the past 50 years. It was initially deemed too toxic by its German discoverers and shelved temporarily. Chloroquine is administered once daily for the treatment of all species of malaria (10mg base/kg on days one and two, 5 mg/kg on day 3). Weekly chloroquine (5mg base/kg) is used for prophylaxis either alone or in combination with proguanil (200mg/day in adults). A fixed-dose combination of chloroquine 100mg and proguanil 200mg is used in some European countries as a daily prophylactic. Other therapeutic uses of chloroquine include the treatment of amoebic liver abscess, rheumatoid arthritis, and systemic or discoid lupus erythematosus. More toxicity is associated with the higher doses that are used for prolonged periods for rheumatology patients than for prophylactic or therapeutic use in malaria.

2.1 Mild and Moderate Adverse Effects

Chloroquine is usually well tolerated when used for treatment or prophylaxis. Commonly reported symptoms include headache, malaise, dizziness, blurred vision, difficulty focusing, mild gastrointestinal upset, and itching.[10] Itching is a particular problem in dark-skinned patients and affects compliance.[11,12] Itching is described as a widespread prickling sensation mostly affecting the palms, soles and scalp, which starts within 6–24 hours and may last for several days. It can be very distressing. Oral antihistamine treatment is not usually very effective. By contrast, in a retrospective study of itching in Thai and Burmese patients with vivax malaria, only 1.9% (23/1189) reported itching that was rated as mild and responded favourably to antihistamine treatment.[13] Less common chloroquine adverse effects include skin depigmentation, whitening of scalp hair and eyebrows, hair loss, various rashes (photoallergic dermatitis, exacerbation of psoriasis, bullous pemphigoid, exfoliative dermatitis, pustular rash, urticaria, fixed-drug eruption), and eye pathology (see section 2.2).[14-19]

Chloroquine prophylaxis, either alone or in combination with proguanil, is well tolerated. In one open-label, prospective study in 384 Scandinavian travellers, adverse effects associated with chloroquine plus proguanil were low: nausea (3%), diarrhoea (2%), and dizziness (1%); all were considered mild.[20] However, larger, retrospective, post-travel studies have recorded considerably higher rates of reported symptoms. One such study collected data from 145 003 travellers who used several regimens while on holiday in Kenya.[21] Non-serious adverse effects were assessed in 89 902 travellers who used no prophylaxis (n = 4026), chloroquine 300mg weekly (n = 3354), chloroquine 600mg weekly (n = 3646), chloroquine + proguanil (n = 20 150), sulfadoxine/pyrimethamine (n = 8673), and mefloquine (n = 50 053). Adverse effects were reported frequently by recipients of all prophylactic regimens and by 5.3% of travellers not on prophylaxis. The corrected rates (reported rate less 5.3%) were 18.5% (chloroquine 300mg), 17.2% (chloroquine 600mg), 30.1% (chloroquine + proguanil), 11.6% (sulfadoxine/pyrimethamine) and 18.7% for mefloquine. Overall, some 50% of adverse effects were mild, 36–40% were moderate, and 10–14% were severe. Nausea was the most common adverse effect for all regimens, reported by 10.8–18.8% of travellers. The chloroquine + proguanil group had the highest proportion of travellers who reported symptoms. The rates for nausea (18.8%) and for mouth ulcers (7.9%), a known adverse effect of proguanil, were the reasons for the overall excess of adverse effects with this regimen. Dizziness was reported by more people taking mefloquine (7.6%) than those taking chloroquine (5–6%), whereas the opposite trend was noted for insomnia. No differences were found between regimens for depression and headaches.

In a telephone survey of returning British travellers, the reporting of any adverse effect was similar for those taking chloroquine + proguanil (n = 1181) and mefloquine (n = 1214), at approximately 40%.[22] Most adverse effects were considered 'trivi-

al' and did not interfere with daily activities. Approximately 0.7% (9/1214) of those taking mefloquine had disabling neuropsychiatric adverse effects (defined as interference with daily activities), compared with 0.09% (1/1181) of those taking chloroquine + proguanil (p = 0.021). Mild gastrointestinal upset was reported more frequently in the chloroquine + proguanil group: 16.3% versus 12.5% (p = 0.009). These findings were broadly similar to a postal survey of visitors to South Africa. People taking chloroquine + proguanil reported more gastrointestinal upset and mouth ulcers, and those taking mefloquine reported more neuropsychiatric effects.[23]

There has been some experience with the fixed combination of chloroquine + proguanil in travellers.[24] The combination was well tolerated in 194 French travellers. Gastrointestinal adverse effects were the most commonly reported, affecting about 10% of travellers. Non-serious neuropsychiatric effects were reported by 2%, a significantly lower rate compared with those taking mefloquine (11.5%; n = 183). Proguanil alone is used occasionally as prophylaxis. Two studies have assessed its tolerability. Mouth ulcers were a particular problem in a cohort study of 470 British soldiers in Belize, affecting 37% (142/382) of those who took chloroquine + proguanil and 24% (21/88) of those who took proguanil alone (relative risk [RR] = 1.56 [95% CI 1.05–2.31]).[25] In a series of Dutch travellers, dizziness and nausea were notable adverse effects compared with travellers who took no prophylaxis; interestingly, there were no reports of mouth ulcers in the 103 proguanil recipients.[26]

2.2 Severe Adverse Effects

Severe toxicity may occur with long-term chloroquine usage (e.g. neuromyopathy, retinopathy) or as an idiosyncratic reaction (e.g. erythema multiforme, bone-marrow toxicity). These reactions are rare.[27-30]

The neuromyopathy is characterised by a progressive weakness and atrophy of proximal muscles that may develop after several weeks, months or years of chloroquine treatment. There may also be clinical symptoms and signs (e.g. sensory loss, reduced tendon reflex briskness) and electromyographic evidence of a neuropathy. Discontinuing chloroquine results in the slow return of function.[27] Irreversible visual impairment resulting from chloroquine-induced retinopathy is a well documented complication of long-term, high-dosage therapy.[31,32] Retinal monitoring is recommended for long-term chloroquine recipients. Cumulative total doses of chloroquine 1g base/kg bodyweight or 50–100g total dose (base) have been associated with retinal damage. Retinopathy has rarely, if ever, resulted from doses recommended for malaria prophylaxis.[33] It would be of significant concern only for those on long-term (>5 years) chloroquine prophylaxis. Patients may report temporal scotomas (words disappear when reading, only one-half of an object is seen), and misty vision. Retinal signs include a pale optic disc, arteriolar narrowing, peripheral retinal depigmentation, macular oedema, retinal granularity and oedema, and retinal pigmentary changes consisting of a circle of pigmentation and central pallor, the so called 'doughnut' or 'bull's eye' macula. Reversible corneal opacities have been reported in 30–70% of rheumatology patients within a few weeks of treatment. Although usually asymptomatic, some patients report photophobia, visual halos around lights, and blurred vision. Chloroquine recipients who report impaired vision should be assessed by an ophthalmologist.

Generalised convulsions have rarely been reported in travellers who took weekly chloroquine prophylaxis. In a case series of four women who developed clonic-tonic fits, all had either a previous history of fits (tonic-clonic, complex, or absence seizures) and/or electroencephalogram (EEG) evidence of a lowered seizure threshold.[34]

2.3 Overdose Toxicity

Chloroquine has a low safety margin and its toxic effects are related closely to the ingested dose. A one-time dose of 20 mg/kg is considered toxic and doses as low as 30 mg/kg have resulted in fatalities.[35] A chloroquine dose of 5g was an accurate predictor of a fatal outcome in adults.[36] Severe clinical features are of rapid onset, occurring between 1–3 hours, and include visual disturbances, vomiting, hypokalaemia (<3 mmol/L) convulsions, drowsiness, shock, cardiorespiratory arrest, and death. The case fatality rate is 10–30%. Diazepam is a specific antidote. Parenteral chloroquine may

cause potentially lethal hypotension. It must never be given by intravenous injection. It should be administered either as a constant-rate infusion or as small (<5mg base/kg) frequent (4- to 6-hourly) intramuscular or subcutaneous injections.[37]

2.4 Use in Pregnant Women

There is now considerable clinical experience of chloroquine use as treatment and prophylaxis in pregnancy. It is considered suitable for use in all three trimesters of pregnancy.[38-41] A recent study of 21 children (age range 12 weeks to 10 years) born to mothers with systemic lupus erythematosus or rheumatoid arthritis who used hydroxychloroquine (n = 14) or chloroquine (n = 7) during pregnancy provide further reassuring data; both drugs were used for a mean of 7.2 (range 1–9) months.[42] Detailed slit lamp and visual field examinations revealed no ophthalmological abnormalities. In another clinical series of 35 children born to mothers who used hydroxychloroquine throughout pregnancy, there were no congenital abnormalities at birth or evidence of developmental delay at 1 year; eight of the 35 were also breast fed for 3–6 months *post partum*.[43] There were no retinal abnormalities detected in 16 children examined at birth and 1 year later. The future role of chloroquine as an antimalarial in pregnancy will be determined by the prevalence and degree of chloroquine resistance. This limits chloroquine use for prevention of *P. falciparum* but *P. vivax* remains generally sensitive in most areas.

2.5 Use in Breast-Feeding Women

Chloroquine is excreted into breast milk in small quantities with a mean half-life of 8.8 days. The dose that a breast-feeding baby would receive was estimated at 0.7% of the daily, maternal dose, and 4.2% over 9 days.[44,45] Chloroquine can be given to breast-feeding mothers.

2.6 Contraindications and Cautions

In practice, the few contraindications to using chloroquine as treatment are known allergy, and unacceptable toxicity from previous use.[46] As prophylaxis, chloroquine is contraindicated in patients with epilepsy, severe renal disease, and severe hepatic disease. The WHO also includes a history of psoriasis.[47] The prophylactic dose of chloroquine should be reduced in patients with mild or moderate renal failure (serum creatinine <700 mol/L) to avoid drug accumulation.[48] Data are lacking on the optimal chloroquine prophylactic dose in liver impairment. In 'mild' liver disease, chloroquine appears to be safe.[49] The British National Formulary (BNF) 'advises caution' in patients with porphyria, psoriasis, myasthenia gravis, and glucose-6-phosphate dehydrogenase (G6PD) deficiency,[46] although there is no convincing evidence that chloroquine causes haemolysis in G6PD-deficient individuals. Chloroquine is listed as a drug that can be used in patients with acute porphyria by the Cardiff Porphyria Service.[50] Low-dosage chloroquine (e.g. 125mg twice weekly) may be used to treat porphyria cutanea tarda by specialists in this field. Chloroquine as prophylaxis and treatment for malaria are contraindicated in porphyria cutanea tarda because of the danger of exacerbating skin lesions and precipitating potentially fatal systemic reactions as a result of the mobilisation of large amounts of porphyrins.[51,52]

The question of chloroquine exacerbating psoriasis has not been answered definitively because psoriasis remits and relapses naturally. There are a number of published reports of exacerbations of psoriasis coincident with chloroquine as antimalarial prophylaxis, and chloroquine or hydroxychloroquine as treatment for rheumatoid and psoriatic arthritis.[14,53-55] Psoriasis should be viewed as a contraindication to chloroquine prophylaxis but as a relative contraindication for treatment.

3. Sulfadoxine/Pyrimethamine

Sulfadoxine/pyrimethamine is a fixed-dose combination that has the advantage of being a one-dose treatment (25 mg/kg based on sulfadoxine) for *P. falciparum* malaria. Fever resolution is slower than with chloroquine or amodiaquine, and resistance has eroded its efficacy.[7] It is now largely ineffective in many parts of Latin America, and South East Asia, where *P. vivax* is also highly resistant. In Thailand it had a useful life span of only 5 years before falling to resistance.[56] Sulfadoxine/pyrimethamine is contraindicated as prophylaxis because of the risk of serious cutaneous and liver toxicity (see sections 3.2.1 and 3.2.2).

Sulfadoxine/pyrimethamine shares toxicity with other sulphonamides. There is also cross-sensitivity between sulphonamides and other chemically related drugs, e.g. sulphonylureas, thiazides and acetazolamide. Rates of mild toxicity associated with sulphonamide treatment are between 10% and 15% in non-AIDS patients.[57] A large number and range of adverse effects have been associated with sulphonamide use but their frequencies are generally not well documented. The following list is presented to allow an awareness of the range of possible sulphonamide-related adverse effects:

- gastrointestinal toxicity: glossitis, stomatitis, pancreatitis, melaena, salivary gland enlargement and pseudomembranous colitis
- skin reactions: itching, urticaria, photosensitivity, cutaneous vasculitis, erythema nodosum, erythema multiforme, lichen planus and hair loss
- CNS: dizziness, ataxia, benign intracranial hypertension, aseptic meningitis, hearing loss, tinnitus, reversible peripheral neuropathy
- haemotological: haemolytic anaemia, megaloblastic anaemia, agranulocytosis, thrombocytopenia
- renal effects: proteinuria, haematuria, acute interstitial nephritis, crystalluria (see section 3.3)
- drug fever[10,46]
- pulmonary eosinophilia.

3.1 Mild and Moderate Adverse Effects

In general, adverse reactions are infrequent and mild when sulfadoxine/pyrimethamine is used for malaria treatment. Commonly reported adverse effects include gastrointestinal upset (abdominal pain, nausea, diarrhoea) and headache. Itching was reported by 12% of patients in one treatment trial in Africa[58] and by 2.1% of Indonesians.[59] In clinical trials sponsored by the WHO/Tropical Disease Research (TDR), sulfadoxine/pyrimethamine was well tolerated in 2400 patients, mostly African children. There was no serious toxicity attributed to sulfadoxine/pyrimethamine.[60]

3.2 Severe Adverse Effects

Several severe adverse effects have been documented with sulfadoxine/pyrimethamine as prophylaxis or treatment.

3.2.1 Cutaneous Toxicity

Sulfadoxine/pyrimethamine has caused erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis.[61-63] These reactions have been well documented following sulfadoxine/pyrimethamine weekly as prophylaxis. Consequently, sulfadoxine/pyrimethamine is no longer recommended for malaria prophylaxis.[64] The estimated risk of these severe cutaneous reactions in American travellers was 1/5000–1/8000 and of a fatal reaction as 1/11 000–1/25 000.[61] Figures from the UK[65] and Sweden[66] were broadly consistent. Risk estimates of cutaneous toxicity were 1/4900 and 1/10 000, respectively, and 1/11 100 and 1/35 000, respectively, for a fatal reaction.[65,66] The case fatality rates in these clinical series were high: 29% (American and Swedish studies),[64,66] and 50% (British study).[65] In Mozambique there were 22 cases of Stevens Johnson syndrome with three deaths among 149 000 persons following the use of sulfadoxine alone for mass prophylaxis against cholera, giving a risk of Stevens Johnson syndrome of 1.5/10 000 and the risk of death as 2/100 000.[67] There were 11 fatal cutaneous reactions among 109 485 persons who received one or more weekly doses of sulfadoxine as prophylaxis against meningococcal disease in Morocco, a rate of 1/10 000 recipients.[68] Three nonfatal cases of Stevens Johnson syndrome were reported among 480 persons in South Africa given sulfadoxine as prophylaxis against *Streptococcus pneumoniae*.[69]

Stevens Johnson syndrome has also been reported in one child following inappropriate, presumptive treatment of malaria.[70] There are no data on the risk of severe skin reactions following sulfadoxine/pyrimethamine treatment but clinical experience suggests that the risk is substantially lower than for sulfadoxine/pyrimethamine as prophylaxis. In western Kenya, the lack of severe cutaneous toxicity seen in young children treated with sulfadoxine/pyrimethamine suggests that this adverse reaction is likely to be rare in this patient population (B. Nahlen, personal communication). The paediatric experience from Malawi is similar (M. Molyneux, personal communication). Another serious skin reaction, erythroderma, has been reported following sulfadoxine/pyrimethamine and chloroquine prophylaxis and presumptive sulfadoxine/pyri-

methamine treatment; the erythroderma was thought to be a result of the sulfadoxine/pyrimethamine.[71]

3.2.2 Hepatic Toxicity

Reported sulfadoxine/pyrimethamine-induced hepatic toxicity includes liver granulomas, a mixed cholestatic-hepatocellular hepatitis, acute hepatic necrosis, and chronic hepatitis.[72-75] The estimated risk of serious hepatotoxicity following sulfadoxine/pyrimethamine prophylaxis was 1/11 100 in UK travellers.[65] Using data from the US FDA and a US-based pharmaceutical database, Zitelli et al. estimated the risk of developing non-fatal hepatotoxicity following sulfadoxine/pyrimethamine treatment as 1/16 000–1/54 000 sulfadoxine/pyrimethamine exposures.[75] Hepatic reactions can occur in conjunction with severe cutaneous toxicity.

3.2.3 Hypersensitivity Reactions

Clinically, these reactions may manifest as a systemic vasculitis, cutaneous vasculitis, acute glomerulonephritis, myocarditis, and various pulmonary reactions, e.g. lung infiltrates, non-cardiogenic pulmonary oedema, pulmonary eosinophilia and allergic alveolitis.[10,76-78] These severe reactions have been documented following sulfadoxine/pyrimethamine, other sulphonamides and pyrimethamine alone. Data estimating the risk of developing these reactions are lacking but they appear to be rare.

3.2.4 Haematological Reactions

Pyrimethamine inhibits dihydrofolate reductase, an enzyme essential for folic acid synthesis. Clinical or subclinical folate deficiency may be exacerbated in vulnerable groups, e.g. malnourished children and pregnant women, and following long-term, high-dose therapy for AIDS-related toxoplasmosis.[79-81]

Reported sulphonamide-induced haematological toxicity appears rare but encompasses a broad range of potential toxicities that include disseminated intravascular coagulation, hypoprothrombinaemia, haemolytic-uraemic syndrome, methaemoglobinaemia, Coomb's antibody-positive haemolysis, antibody-mediated thrombocytopenia, and eosinophilia. Acute haemolysis may occur in G6PD-deficient patients. Data are lacking but clinical experience of sulfadoxine/pyrimethamine use from Malawi, a country of type A^- (African) G6PD deficiency, suggests haemolysis is unusual (M. Molyneux, personal communication).

A detailed retrospective study from the UK and Sweden examined the reported adverse reactions to ten sulphonamide drugs.[82] A total of 8339 reactions were reported over 20 years (1968–1988). Of these, 1272 (15%) were blood dyscrasias, 3737 (45%) were dermatological, and 578 (7%) were hepatic. Of these, 3525 (42%) were classified as serious. Some 90% of all blood dyscrasias were serious. The case fatality rate of any serious reaction was 6.7%. This was highest in patients with white blood cell dyscrasias (14.3%), followed by skin (9%), and hepatic reactions (4.2%). Sulphonamides with longer elimination half-lives ($t_{1/2}\beta$) had higher case fatality rates. Skin reactions induced by sulfadoxine/pyrimethamine ($t_{1/2}\beta$ 9 days) had a case fatality rate of 33% compared with 10% for cotrimoxazole (trimethoprim-sulfamethoxazole; $t_{1/2}\beta$ 6–12 hours); corresponding rates for white cell dyscrasias were 20% and 11%, respectively. Based on the Swedish data, the estimated rates of any serious sulphonamide-induced reactions were between 9 and 33/100 000 short-term recipients (2 weeks), between 53 and 111/100 000 recipients of sulfadoxine/pyrimethamine for malaria prophylaxis, and between 1744 and 2031/100 000 patients taking continuous therapy, e.g. sulfadiazine.

3.3 Overdose Toxicity

Published data on sulfadoxine/pyrimethamine overdose are scant.[83,84] As a class, sulphonamide overdoses are characterised by acute gastrointestinal symptoms (abdominal pain, nausea, severe vomiting, and haematemesis) and acute CNS effects (within 30 minutes to 2 hours). Initially there is excitability and convulsions, followed by respiratory depression, shock, coma, and death. Other toxic effects include bone-marrow depression, megaloblastic anaemia, glossitis, and crystalluria; the risk of crystalluria with sulfadoxine is minimal because of its high solubility and very low renal excretion.[35] There is no specific antidote. Early gastric lavage and supportive care are recommended. Sulfadoxine excretion may be increased by alkalinisation of urine. Diazepam should be used for the treatment of convulsions and folinic acid 5–15 mg/day should be given for at least 3 days for

marrow rescue. Renal function and routine haematology should be checked weekly for 4 weeks after the overdose.

3.4 Use in Pregnant Women

Where it is still effective, sulfadoxine/pyrimethamine has an important role in the prevention of the deleterious effects of malaria in pregnancy in areas of high malaria transmission, where maternal anaemia and low birthweight babies are the two main problems. The regimen employed in HIV-negative mothers is one dose of sulfadoxine/pyrimethamine in the second and one dose in the third trimester of pregnancy in primigravidae, so-called intermittent preventive treatment. Studies from Kenya and Malawi have shown good efficacy in reducing placental parasitaemia, and variable effects on maternal anaemia and low birthweight babies.[85-87] HIV seropositivity is associated with higher rates of maternal and placental parasitaemia in women of all parities.[88] Sulfadoxine/pyrimethamine administered monthly to HIV-positive primigravidae and secundigravidae was required to achieve comparable outcomes to intermittent sulfadoxine/pyrimethamine in HIV-negative women from western Kenya.[89] In these studies (total number of women = 3000), sulfadoxine/pyrimethamine was well tolerated, and there was no difference in reported maternal adverse events as a function of HIV serological status. There were no cases of congenital malformation. The proportion of clinically confirmed jaundiced neonates ranged from 0% (n = 1245),[85] to 15% (n = 1335).[89] In the latter study, jaundice was not associated with sulfadoxine/pyrimethamine consumption within 30 days of delivery, or the consumption of at least one dose of sulfadoxine/pyrimethamine, or detectable sulpha compounds in maternal urine at delivery. This reassuring outcome is of importance because of the anxiety over the theoretical risk of sulphonamide displacement of conjugated bilirubin *in utero* that might result in the development of kernicterus.[90]

Published data on sulfadoxine/pyrimethamine use in the first trimester of pregnancy are limited. Animal toxicology studies show dose-related toxicity of pyrimethamine in the form of fetal resorption and growth retardation that were prevented by folic acid administration.[91] There is a case report of a French woman who delivered a child with severe congenital abnormalities (missing left arm, exteriorisation of the abdominal and thoracic organs) who took chloroquine before and after conception and three doses of dapsone/pyrimethamine after conception as prophylaxis.[92] The authors thought that the congenital malformation was related to the dapsone/pyrimethamine. Sulphonamides are not teratogenic in humans.[39] Pyrimethamine use in the past for mass prophylaxis was not apparently associated with congenital abnormalities.[93] In a study of travellers who had been accidentally exposed to sulfadoxine/pyrimethamine or mefloquine as prophylaxis in the first trimester of pregnancy, the rates of congenital abnormalities were 7.0% (12/172 [95% CI 3.6–11.9]), and 3.8% (16/421 [95% CI 2.2–6.1]), respectively.[94] These reported rates of congenital abnormalities were comparable to background rates and provide some reassurance. Although not directly applicable to malaria in pregnancy, the limited published data on the use of sulfadoxine/pyrimethamine for the treatment of toxoplasmosis in pregnancy indicate a favourable outcome for children in terms of a reduction in the severe forms of congenital toxoplasmosis.[95]

3.5 Use in Breast-Feeding Women

Both pyrimethamine and sulfadoxine are excreted into the breast milk.[96] In a study of three women given concurrent chloroquine and dapsone/pyrimethamine, the secretion of all three drugs was low and deemed harmless to the infant.[45] Although sulfadoxine secretion is low it carries the theoretical risk of precipitating kernicterus in jaundiced and/or premature neonates (by sulphonamide displacement of conjugated bilirubin),[90] and haemolysis in G6PD-deficient neonates.

Substantial experience of prescribing sulfadoxine/pyrimethamine to breast-feeding women in Malawi has shown that sulfadoxine/pyrimethamine is well tolerated by both mothers and breast-fed infants. Sulfadoxine/pyrimethamine is still given to mothers even if the infant is <2 months old or is jaundiced. Acute haemolysis has not been observed in breast-fed infants (M. Molyneux, personal communication). Clinical experience from western Kenya also suggests that sulfadoxine/pyrimethamine use in breast-feeding women has caused no ill ef-

fects in breast-fed infants (B. Nahlen, personal communication). There is a need to document carefully the use of sulfadoxine/pyrimethamine in breast-feeding women in order to collect more safety data.

There are insufficient data to make a definitive recommendation regarding sulfadoxine/pyrimethamine use in breast-feeding mothers. However, given the favourable albeit anecdotal evidence from Africa, breast-feeding should not be interrupted but mothers should be warned of the possible adverse effects.

3.6 Contraindications and Cautions

Sulfadoxine/pyrimethamine is contraindicated in patients with known allergy to sulphonamides or related compounds (e.g. thiazides, see section 3), acute haemolysis following previous sulphonamide use, patients with confirmed folate deficiency, severe renal disease, and severe hepatic disease. As a class, sulphonamides should not be administered to neonates aged <6 weeks because of the possible risk of causing haemolysis (as a result of their relative G6PD deficiency) and kernicterus (via displacement of conjugated bilirubin).[90] However, recent data from India have shown that the use of cotrimoxazole (trimethoprim-sulfamethoxazole) for neonatal sepsis is not associated with these problems.[97] The same may well apply to sulfadoxine/pyrimethamine. A review of the pertinent data is needed to see how much evidence this recommendation is based upon. Clinicians may use sulfadoxine/pyrimethamine in young neonates if potentially better alternatives are unavailable. As a class, sulphonamides may precipitate acute porphyric crises in individuals with acute porphyria, and should not be used.

4. Mefloquine

Mefloquine, a quinoline methanol with similarities to quinine, is effective against the asexual stages of malaria. However, resistance by *P. falciparum* is present in parts of South East Asia, and parts of the Amazon region.[98,99] In Africa, reports of mefloquine resistance have largely been from *in vitro* studies and prophylactic failures in non-immune travellers.[100,101] Mefloquine is a very effective prophylactic drug when used appropriately.[102,103] The recommended treatment dose of mefloquine is either 15 mg/kg as one dose or preferably a split dose of 25 mg/kg; the 10 mg/kg dose is given after 6–24 hours. The prophylactic dosage is 250mg weekly (adults) and 5 mg/kg for children. Mefloquine prophylactic failures should not be treated with mefloquine or halofantrine because of the risk of increased mefloquine toxicity, and halofantrine-related cardiotoxicity, respectively.[104]

4.1 Treatment-Associated Toxicity

Mefloquine is generally well tolerated by malaria patients.[105] However, in some treatment trials, mefloquine recipients reported a higher rate of certain adverse effects compared with chloroquine (dizziness), halofantrine (nausea, vomiting, fatigue and dizziness) and artemether/lumefantrine (nausea, vomiting, dizziness, insomnia).[106-109] Comparing mefloquine-containing regimens with drugs such as artemether/lumefantrine or atovaquone/proguanil allows differentiation of drug- and disease-related effects. Thus, of those reporting significant gastrointestinal or CNS symptoms, approximately two-thirds can be ascribed to mefloquine and one-third to the malaria.

In a review of mefloquine treatment in 3673 patients of all ages living along the Thai-Burmese border, the most important adverse effect was early (≤1 hour) drug-induced vomiting,[110] a finding seen in other studies. Other important dose-related adverse effects were anorexia, nausea, late vomiting and dizziness.

Early vomiting can be a particular problem that compromises treatment efficacy even if mefloquine is readministered.[111] Early vomiting is more likely to occur in: (i) sicker patients at presentation (oral temperature >38°C, parasitaemia >10 000/μL); (ii) patients with a history of vomiting within 24 hours of presentation; (iii) young children (≤6 years); and (iv) older adults (>50 years). Children aged ≤2 years had the highest rates of vomiting: 30% (32/106) with high-dose mefloquine (25 mg/kg), and 20% (20/101) with low-dose mefloquine (15 mg/kg). Children aged 3–4 years of age and 5–6 years of age had vomiting rates of 17% and 13%, respectively, with high-dose mefloquine, and 12% and 5%, respectively, with low-dose mefloquine. Vomiting of the repeat dose was also a function of age. In the children aged ≤ 2 years, 14% (high-dose) and 7.5%

(low-dose) vomited after mefloquine re-administration. Splitting the mefloquine dose reduced the overall risk of vomiting by 43%. Vomiting was also reduced 2-fold in patients who received an artemisinin derivative that was followed by mefloquine on the second day of treatment. These findings were confirmed in another study of children aged <5 years from the same population.[112] Of 121 recipients of high-dose mefloquine, 35 (29%) had early vomiting, and 19/101 (19%) vomited following low-dose mefloquine. When given together with an artemisinin derivative, the risk of early vomiting was not increased, whereas delaying the administration of mefloquine (days 2–4) after the artemisinin reduced early vomiting 3-fold (RR = 3.1 [95% CI 1.9–5.3]) despite increased mefloquine levels.[113] However, early vomiting still occurred in 11 of 42 children (26%) aged <30 months who received delayed mefloquine even though by then most children were afebrile and aparasitaemic. Early vomiting with mefloquine 25 mg/kg was not reduced by actively reducing body temperature to <38°C with paracetamol (acetaminophen) and tepid sponging.[114] In Malawi, early vomiting occurred in 29% of 56 children aged <5 years treated with mefloquine 25 mg/kg (single-dose) and 40% of 65 receiving mefloquine 15 mg/kg. Seven (13%) in the high-dose group and 5 (8%) in the low-dose group vomited the repeat dose.[115] Early vomiting was associated with reduced mefloquine absorption on day 2 (blood concentrations <500 μg/L), and an increased risk of persistent parasitaemia on day 7. Mefloquine-induced early vomiting is a significant clinical problem when treating malaria in young children.

ter Kuile et al.[111] also found that high-dose (25 mg/kg) mefloquine produced a significant increase in moderate dizziness (feeling of swaying) and severe dizziness (inability to walk unaided) in children and adults. Between day 1 and day 3, moderate and severe dizziness increased from 1.6% to 6%, and from 0% to 3%, in children, respectively; corresponding figures for adults were 2.6% to 15%, and 0% to 5%. Severe dizziness usually lasted 1 day and had resolved completely within 3 days. Insomnia was present in 1% (n = 336) on day 0; this proportion rose to 4.3% after mefloquine 25 mg/kg and resolved by day 7. General malaise, headache, abdominal pain, diarrhoea, myalgia, and arthralgia were also reported but these symptoms were closely related to the malaria and not caused by the mefloquine.

Other mefloquine treatment studies have been broadly consistent with that of ter Kuile et al.[111] but some studies have found diarrhoea to be mefloquine related.[116] As prophylaxis, mefloquine may cause a variety of mild symptoms that may be masked in malaria patients; these include abdominal pain, diarrhoea, headache, dizziness and general malaise.

4.2 Neuropsychiatric Toxicity Associated with Treatment or Prophylaxis

Much attention has focused on the neuropsychiatric effects of mefloquine. Several reviews have summarised the data.[117-119] A neuropsychiatric event includes any CNS or psychiatric symptom (e.g. headache, dizziness, insomnia, nightmares, anxiety) or illness and a serious neuropsychiatric event encompasses the following principal diagnoses: convulsions, disturbance of consciousness, acute confusion, inability to walk unaided because of vertigo or ataxia, psychosis, disorder of affect, and acute neurosis. Dizziness and anxiety are the most frequently reported neuropsychiatric adverse effects.[120] Predisposing factors are a past history of neuropsychiatric disorders, recent (within 2 months) mefloquine exposure, previous mefloquine-related neuropsychiatric adverse effects, and previous treatment with psychotropic drugs. It is unclear if a family history is a risk factor.

Published data on treatment-related neuropsychiatric adverse effects come from some 20 trials, totalling 25 000 patients, most of whom (21 500) are ethnic Karen living on the Thai-Burmese border. The estimated risks of developing a serious neuropsychiatric adverse effect were: (i) 1/200 European travellers; (ii) 1/159 Nigerian patients (n = 303 children, 14 adults); and (iii) 1/1754 treatments in the Karen.[121-123] More recent data in the Karen have shown these effects to be dose related: 1/2089 (mefloquine 15 mg/kg), and 1/1217 (mefloquine 25 mg/kg).[117] It is not known why the Karen have a lower risk of serious neuropsychiatric adverse effects than other groups. The risk of a serious neuropsychiatric adverse effect increases substantially if mefloquine is used as retreatment for a mefloquine treatment failure or in the recovery stage of severe

malaria.[124,125] Mefloquine should not be given to patients recovering from cerebral malaria.

The data on neuropsychiatric adverse effects during mefloquine prophylaxis have been collected in tourists and soldiers using different study designs. The larger series have been questionnaire studies of returning travellers.[20-23,26,126] Prospective, open-label studies have examined the use of mefloquine alone (i.e. without a comparator) and mefloquine versus other regimens.[24,127-130] Placebo-controlled trials have been conducted in Africa and Asia.[102,131-133] Reports to the drug manufacturer complement formal trials.[134] Essential points from these studies are:

- many (40%) neuropsychiatric adverse effects occur soon after the first dose and 75% are manifest by the third dose
- most are of mild or moderate severity and resolve completely
- some require medical management including hospitalisation
- <2% of patients have sequelae
- women are more likely to experience neuropsychiatric adverse effects
- mefloquine in soldiers (fit, young men) is well tolerated, including the loading dose of mefloquine (250 mg/day for 3 days)
- in prospective studies, mefloquine-related neuropsychiatric adverse effects were broadly similar to other antimalarials or placebo
- long-term mefloquine prophylaxis is well tolerated
- the risk of serious neuropsychiatric adverse effects during prophylaxis is estimated to be 1/10 600 for mefloquine and 1/13 600 for chloroquine.
- In a meta-analysis of controlled trials, mefloquine recipients were more likely to withdraw from studies compared with placebo but not when compared with other prophylactic regimens.[135]

A number of studies have examined psychomotor function, motor function, action requiring fine coordination, and balance and hearing. Boudreau et al. found no compromise of performance of American soldiers who took weekly mefloquine (preceded by the loading dose) or chloroquine as prophylaxis despite more of the former reporting sleep disturbances, increased dream activity and depressed feelings.[133] In a double-blind, placebo-controlled, crossover study of 23 Swiss trainee pilots (mean age 27 years), mefloquine was given as a loading dose, followed by weekly administration for 3 weeks.[136] This regimen was well tolerated but one trainee who reported dizziness, diarrhoea, and flu-like symptoms during the loading-dose phase was withdrawn from the study. There were no significant differences in flying performance, psychomotor functions, and postural sway between the two arms. Poorer sleep quality was reported by the mefloquine recipients, who had a lower mean reduction in sleep times of 34 minutes that was not statistically significant compared with placebo. Similar findings were reported in another placebo-controlled trial of mefloquine prophylaxis and the effect of alcohol when driving a car. There was no impairment of driving in a cohort of young volunteers who had blood levels of alcohol of between 0.3 and 0.5 mg/mL.[137] In ten volunteers, mefloquine had no effect on audiometry and vestibular functions assessed using posturography and nystagmus recording.[138] These data are evidence of the lack of interference of higher mental function in these cohorts.

Two studies have examined tolerability of long-term prophylaxis. Mefloquine was well tolerated in 2289 Dutch marines stationed in Cambodia for 6 months; one battalion of 754 was given a loading dose of mefloquine.[129] Seven soldiers (0.3%) sought medical care for serious adverse events: convulsions (n = 2), myoclonus (n = 1), severe dizziness (n = 2), and skin rash (n = 2). Six changed to doxycycline and one was given mefloquine biweekly with good effect. By questionnaire, 609 (30.2%) of 2015 reported 820 symptoms chiefly headache, concentration disorders, weakness, dizziness, and nausea. Mefloquine given weekly was also well tolerated by 802 American Peace Corps volunteers, of whom 152 used mefloquine for >1 year.[103] The reporting of adverse effects by these volunteers decreased significantly over time from 44% after 4 months' use to 19% after >1 year of use, suggesting that mild symptoms were well tolerated. Only seven (0.9%) stopped prophylaxis because of mefloquine-related toxicity. These data show that mefloquine tolerability was acceptable over the medium to long term.

4.3 Other Adverse Effects

Cutaneous toxicity with mefloquine is rare. In a review of published data from 1983–1997, only 74 cases of any skin reaction were reported. These reactions included itching, red maculopapular rashes, urticaria, cutaneous vasculitis, exfoliative dermatitis, Stevens Johnson syndrome, toxic epidermal necrolysis and severe facial lesions. Pruritus (4–10%) and maculopapular rashes (30%) were the most commonly reported reactions.[139]

Mefloquine is not generally associated with cardiovascular toxicity.[116] Reports of sinus bradycardia and sinus arrhythmia are more likely to be related to resolution of malaria, especially in young fit individuals. There have been reports of complete atrioventricular block (with mefloquine treatment),[140] atrial flutter with 1 to 1 conduction (mefloquine prophylaxis),[141] and aberrant atrioventricular conduction (mefloquine prophylaxis).[142]

Acute intravascular haemolysis has been reported with malaria treatment in expatriate Europeans.[143,144] Agranulocytosis has also been reported.[145] Mefloquine causes transient elevation of transaminases but is rarely associated with hepatitis.[116,146]

4.4 Overdose Toxicity

Published data are confined to a small number of those taking prophylaxis, some of whom also took chloroquine and sulfadoxine/pyrimethamine. An acute encephalopathy was a prominent feature.[84,147]

4.5 Use in Pregnant Women

Mefloquine has been used as both prophylaxis and treatment in pregnant women. Mefloquine prophylaxis (post first trimester) was highly effective and well tolerated in Malawi and on the Thai-Burmese border.[41,148,149] As treatment, most experience comes from western Thailand where increasing mefloquine resistance has necessitated the use of combinations with the artemisinin derivatives (see section 9).[150] A retrospective study from this area showed that mefloquine treatment at any time during pregnancy was associated with a higher risk of stillbirth compared with either quinine monotherapy or other antimalarial drugs.[151] The proportions of stillbirths were 9/200 (4.5%) mefloquine recipients vs 10/633 (1.6%) quinine recipients (odds ratio [OR] = 4.72 [95% CI 1.7–12.7]), vs 12/873 (1.4%) of women who received other drugs (OR = 5.1 [95% CI 2–13.1]). Mefloquine was not associated with an increased risk of abortion, low birthweight, neonatal neurological retardation or congenital malformations. An earlier prospective, prophylactic study (weekly mefloquine after week 24 of gestation) found a nonsignificant increased risk of stillbirth in the mefloquine recipients (n = 159) compared with placebo (n = 152): 7% vs 2.6% (RR = 2.63 [95% CI 0.86–8.08]).[149] No specific cause of the stillbirth in mefloquine recipients could be established. In Malawi, of 1015 evaluable women treated with mefloquine (750mg, followed by 250mg mefloquine weekly), 37 (3.6%) had stillbirths, a rate similar to chloroquine recipients, 3.8% (119/3132). Many women reported drug-related adverse effects (itching, dizziness, gastrointestinal upset); 60% in both groups. Mefloquine recipients were more likely to report dizziness but less likely to report itching (details not given). One mefloquine recipient developed self-limiting, acute confusion (0.098% [95% CI 0.0–0.55]).[41] The role of mefloquine as an antimalarial treatment in pregnancy should remain under careful review.

In a postmarketing survey of 1627 women from Western countries who had been exposed to mefloquine as prophylaxis, there were 32 cases of a congenital malformation, and 79 cases of spontaneous abortions. All congenital abnormalities occurred in women who had taken mefloquine before becoming pregnant or within the first trimester of pregnancy.[152] In a retrospective study of mefloquine prophylaxis in US Servicewomen (n = 72), spontaneous abortions numbered 12; all occurred between 6–12 weeks of gestation. Excluding women with unknown pregnancy (n = 19) and fetal outcomes (n = 17), the stillbirth rate was 12/36 = 33.3% (95% CI 19.5–49.8). There were no congenital abnormalities.[153] These two studies are open to bias and cannot establish definitively a cause and effect relationship between mefloquine use and the subsequent development of congenital malformations, abortions or stillbirths. However, these data raise the possibility that mefloquine use in the first trimester of pregnancy could pose a risk. Therefore, the recommendations that mefloquine prophylaxis should not be

used in the first trimester and that women should not become pregnant within 3 months of stopping mefloquine prophylaxis are still pertinent.

4.6 Use in Breast-Feeding Women

Mefloquine is excreted into breast milk in small amounts, the activity of which is unknown.[154] Circumstantial evidence suggests that adverse effects do not occur in breast-fed infants whose mothers are taking mefloquine.[155] Mefloquine use on the Thai-Burmese border has not been associated with apparent ill effects in breast-fed infants. (R. McGready, personal communication).

4.7 Contraindications and Cautions

Mefloquine should not be given to patients with known allergy to mefloquine or quinine or previous mefloquine-related serious toxicity. Prophylactic contraindications include: (i) current or past epilepsy; (ii) current or past history of psychiatric disease (e.g. depression, bipolar affective disorder, any psychotic disease, severe anxiety neurosis); (iii) the first trimester of pregnancy (women should also avoid pregnancy 3 months after mefloquine use); and (v) severe hepatic disease. The WHO advises against using mefloquine prophylaxis in certain occupations that require a high degree of manual dexterity and co-ordination, e.g. pilots, coach drivers.[47] Treatment contraindications are: (i) epilepsy or psychiatric disease (as above); (ii) mefloquine treatment within the past 2 months; (iii) after severe malaria; (iv) pregnant women in the first trimester (unless no other choice is available); and (v) concurrent halofantrine treatment. Mefloquine should be used with caution in individuals with cardiac conduction disorders.

5. Quinine

Quinine is used for the treatment of uncomplicated, drug-resistant *P. falciparum* and severe falciparum malaria. As monotherapy, quinine has to be given for 7 days to achieve cure but because of its unpleasant adverse effects, patient adherence is often poor. In the treatment of severe malaria, a loading dose of 20mg of the dihydrochloride salt/kg of quinine is required to achieve rapidly parasiticidal drug concentrations; this can be administered by intramuscular injection (split dose; anterior thigh) or by intravenous infusion.[156] Quinine must never be given as a bolus intravenous injection as this may cause fatal hypotension or cardiac arrhythmias.

5.1 Adverse Effects

Oral quinine in standard dosages (10 mg/kg 8-hourly) is associated with cinchonism, a constellation of minor but unpleasant adverse effects consisting of nausea, headache, tinnitus, mild, high-tone hearing impairment, dysphoria, and blurred vision. Almost all patients treated with quinine report cinchonism.[10] More unpleasant symptoms such as vomiting, abdominal pain, diarrhoea, and vertigo may also occur. When used in severe malaria, quinine commonly causes hyperinsulinaemic hypoglycaemia. Specific adverse effects are mentioned in the following sections.

5.1.1 Eye and Auditory Toxicity

Ototoxicity is a well-recognised adverse effect of quinine. Hearing loss in Thai adults (n = 10) affected the high-tone range, was rapid in onset, not always clinically apparent, and resolved spontaneously.[157] Tinnitus, detected after quinine plasma levels exceeded 5 mg/L, was not related to the degree of audiogram-measured hearing loss. In a study comparing healthy volunteers (n = 12) and patients with malaria (n = 10), hearing loss was audiometrically documented in nine healthy volunteers and all patients. Hearing loss in the volunteers, who received quinine 300mg, was more often in the high-frequency range, occurred at a mean total peak concentration (C_{max}) of 2 mg/L (standard deviation [SD] = 0.5), and was not always clinically manifest. All patients, who received quinine 600mg 8-hourly, experienced ototoxic symptoms. Hearing loss was in the high- and standard-frequency range, and was maximal on the third day of treatment. Full recovery of hearing was achieved for both groups.[158]

Serious toxicity has been reported very rarely. Transient and permanent blindness has been documented in a small number of patients with uncomplicated or severe malaria, most of whom were overdosed.[159-161] The incidence in severe malaria is <0.1%.

5.1.2 Hypoglycaemia

Hypoglycaemia is a significant adverse effect, affecting up to 10% of patients with severe malaria given quinine, and is mediated through a quinine-induced increase in insulin secretion.[162,163] This is amplified in pregnancy. Profound hypoglycaemia occurs in 50% of pregnant women with severe malaria treated with quinine and may be particularly difficult to manage.[164] Typical symptoms may not be clinically obvious in unconscious patients and may be missed if regular blood glucose measurements are not performed. Hypoglycaemia may cause a change in behaviour, tachypnoea, convulsions, and deepening coma.[165] Hypoglycaemia also occurs in pregnant women with uncomplicated falciparum malaria and has been reported occasionally following oral quinine for malaria or leg cramps.[166,167]

5.1.3 Cardiac Effects

Quinine should never be given by intravenous injection as potentially lethal hypotension may result from transiently high plasma concentrations in the distribution phase. Iatrogenic hypotension does not occur with carefully rate-controlled infusions or following intramuscular injection. Quinine may cause lengthening of the QTc interval that is mainly a result of QRS widening; JT intervals are usually normal, making quinine less arrhythmogenic than quinidine.[168] Nevertheless, there continues to be anxiety regarding use of the quinine loading dose in patients who have previously received quinine or mefloquine. Extensive experience from Thailand and Vietnam has shown that patients with a history of quinine or mefloquine consumption were not adversely affected by the quinine loading dose (N.J. White, unpublished observations).[169] Two studies have examined the cardiac interaction of mefloquine and quinine. In seven human normal volunteers, the increase in QTc was similar between quinine and quinine combined with mefloquine. There was a positive correlation between the increase in QTc and the total and free quinine concentrations but no correlation between the QTc interval increase and the mefloquine concentrations.[170] In 13 malaria-treated patients, quinine combined with mefloquine produced a modest increase in the QTc interval. No patient had a QTc interval >0.5s.[171] These data show the absence of a clinically significant cardiac interaction and support the use of a quinine loading dose even with a recent history of mefloquine use. There has been a report of an elderly Caucasian woman who died of ventricular fibrillation while receiving intravenous quinine. She had a slightly prolonged QTc interval on admission that increased during treatment and was caused by unexpectedly high free quinine levels.[172] This case report contrasts with the extensive use and lack of cardiovascular adverse effects with a quinine loading dose in randomised, controlled clinical trials enrolling nearly 2000 patients.[173]

5.1.4 Haematological Reactions

Quinine-induced thrombocytopenia was reported in 43 patients in Sweden and 11 from the US over 11 and 9 years, respectively, making this adverse effect very rare.[174,175] Thrombocytopenia has nevertheless caused fatalities.[176] Thrombocytopenia has also been reported following ingestion of tonic water water (which contains approximately 80 mg/L of quinine).[177,178] Leucopenia and thrombocytopenia were reported in one patient following quinine use for nocturnal cramps.[179] Acute intravascular haemolysis, caused by various mechanisms, has often been labelled 'blackwater fever'. However, this clinical picture in the tropics is more often caused by infections or haemolytic drugs (e.g. primaquine) given to patients with G6PD deficiency.[180,181] Quinine can cause the haemolytic-uraemic syndrome, disseminated intravascular coagulation (DIC), and DIC with renal failure.[182-186]

5.1.5 Cutaneous and Hepatic Toxicity

Various skin reactions are associated with quinine. Pruritus, skin flushing, and urticaria are the most common manifestations of quinine hypersensitivity. Other rashes, reported rarely, have included photosensitivity, cutaneous vasculitis, lichen planus, and lichenoid photosensitivity.[187-191] A small number of case reports have documented granulomatous hepatitis.[192,193]

5.2 Toxicity of Intramuscular Quinine

Intramuscular quinine, administered in the anterior or lateral thigh, is a satisfactory alternative to intravenous quinine if venous access is problematic.[194,195] More dilute solutions (e.g. 60 mg/mL) are less painful than undiluted quinine (300 mg/mL), and less likely to cause sterile abscesses or muscle

necrosis. One particular serious complication of quinine injections is tetanus, a complication known to Ross in the early 20th century.[196] In a retrospective study from southern Vietnam, Yen et al. reported a higher risk of developing tetanus after intramuscular quinine, a higher case fatality rate, and a more rapid death compared with other causes of tetanus.[197]

5.3 Quinine Pharmacokinetics and Toxicity

Quinine is highly protein bound, principally to α_1-glycoprotein.[198] The free (unbound) quinine determines its biological effects and accounts for approximately 10% of the total plasma quinine concentration. In uncomplicated malaria, cinchonism is associated with a total plasma quinine concentration >5 mg/L.[199] The mean C_{max} quinine concentration of the 20 mg/kg loading dose in adults with severe malaria is between 15 and 16 mg/L. Despite this, and levels that may also exceed 20 mg/L, significant toxicity is rare due to the increase in α_1-glycoprotein and thus reduced free fraction.[200-203] Defining the optimal dose of quinine in areas of different quinine sensitivity has been subject to debate.[204,205] Because the risks of undertreatment in severe malaria (i.e. death) outweigh the very rare serious cardiovascular or nervous system adverse effects, the WHO recommends the 20 mg/kg loading dose, irrespective of the local *in vitro* quinine sensitivities.[165]

In Gambian children aged <2 years with severe malaria, the pharmacokinetic profiles of intramuscular and intravenous quinine (loading dose of 20 mg/kg, then 10 mg/kg 12-hourly) were similar to those in older children and adults; mean, peak total quinine levels were 16.4 mg/L (intramuscular) and 17.5 mg/L (intravenous). Free quinine levels at 4 hours post-administration ranged from 0.27 to 1.89 mg/L. There were no cases of quinine-induced hypoglycaemia but mean glucose levels were significantly lower at 4 hours. There were no significant changes in the QTc intervals, but there were increases in the QRS intervals at both 2 hours (15.6%) and 4 hours (17.3%) compared with baseline; these were independent of both total and free quinine levels. These changes were not seen in nine children aged 2–10 years of age. The authors concluded that very young children may be more susceptible to quinine toxicity.[206] More work is needed in this area.

5.4 Overdose Toxicity

Quinine overdose produces a wide range of dose-related effects.[207-210] Cinchonism is invariable. CNS features include impaired consciousness, coma, and convulsions, especially in children. Toxic amblyopia (visual field defects), blurred vision, fixed dilated pupils, visual field constriction, altered colour perception, and blindness are the documented ophthalmic changes. Many patients are left with some visual impairment and a minority remain blind. Fundoscopy may be normal or become abnormal only after blindness is resolving. Signs include disc pallor, retinal arteriolar vasospasm, venous dilatation, and retinal and macular oedema. Fluorescein angiography may show narrowing of the retinal arterioles and a slight reduction of capillaries on the optic disk. The electroretinogram and visual evoked potentials give results consistent with optic nerve damage that recover concomitantly with the recovery of visual acuity.[211,212] Stellate ganglion block has been tried in the past to relieve blindness but without success.[213] Hyperbaric oxygen showed promise in two patients with quinine-induced blindness.[214] ECG signs of quinine overdose include sinus tachycardia, prolonged PR interval, bundle branch block, widening of the QRS complex, increased QTc interval, ST segment depression, and T-wave inversion. Ventricular tachycardia and idioventricular rhythm are usually associated with cardiogenic shock. Hypokalaemia, an independent risk factor for ventricular arrhythmias, may also be present.

Defining a lethal dose of quinine is difficult. Fatalities have occurred after the consumption of 2–8g in previously healthy adults and up to 2.4g in children.[35] Total, plasma quinine concentrations have varied at the time of patient admission from <10 mg/L up to approximately 35 mg/L).[207-209] Levels >15 mg/L were associated with increased risks of visual disturbances and cardiac arrhythmias.[209] These total plasma concentrations cannot be extrapolated to malaria because increased plasma protein binding reduces the free biologically active fraction. Treatment involves supportive measures, e.g. inotropes for circulatory failure. Gastric lavage is of doubtful value given that vomiting usually occurs before admission and that quinine is rapidly

absorbed. Activated charcoal is a useful method of quinine removal.

5.5 Use in Pregnant and Breast-Feeding Women

Quinine has been used in the past to induce abortions but this resulted in significant maternal morbidity and mortality, and possible congenital abnormalities of the auditory and optic nerves.[215] However, evidence for the latter has been strongly contested. The weight of evidence suggests that therapeutic doses of quinine are relatively safe in pregnancy, apart from its propensity to cause hypoglycaemia. In the treatment of malaria in late pregnancy, quinine actually reduces uterine contractions by treating the infection which increased uterine excitability.[164,216-218]

Quinine crosses the placenta and is excreted into breast milk.[219] The mean quinine concentration in umbilical cord blood and breast milk is about 30% of the maternal concentration. Quinine at therapeutic doses is suitable for use in pregnant and breast-feeding women.

5.6 Contraindications and Cautions

Quinine should not be given to patients known to be allergic to quinine or other cinchona alkaloids. This also includes quinine hypersensitivity to quinine-containing foods and drinks. Relative contraindications include: (i) myasthenia gravis (quinine-induced exacerbation); (ii) optic neuritis; (iii) tinnitus; and (iv) acute haemolysis.[10,46] Quinine should be used with caution in hepatic disease and in cardiac disease, e.g. atrial fibrillation, conduction defects, heart block. Patients with severe malaria and prolonged QTc intervals on admission should be monitored closely. Important drug interactions with quinine include prochlorperazine,[220] cisapride, antihistamines and halofantrine (increased QTc interval), digoxin (increased levels of digoxin), cimetidine (reduced quinine clearance and increased quinine levels), and rifampicin (increased quinine clearance).

6. Halofantrine

Halofantrine, a phenanthrene methanol, is effective against the blood forms of chloroquine-resistant *P. falciparum* and chloroquine-resistant *P. vivax*.[221,222] However, halofantrine resistance and treatment failures because of poor drug absorption, have been reported for *P. falciparum* in Africa and on the Thai-Burmese border.[107,223,224] The dosage in adults is 500mg 6-hourly for three doses (total first course dose 1500mg), and in children weighing >10kg is 8mg base/kg at 6-hourly intervals for three doses. A second course of therapy is recommended by the manufacturer 1 week after the initial treatment in non-immune patients to ensure radical cure of *P. falciparum*. Halofantrine has several disadvantages that include variable bioavailability, cross-resistance to mefloquine, potentially serious cardiotoxicity and the impractical second dose for non-immune patients.

6.1 Mild and Moderate Adverse Effects

Clinical experience has shown that halofantrine is generally well tolerated. Gastrointestinal adverse effects, e.g. nausea, vomiting, abdominal pain and diarrhoea, are rare.[225] Hepatic toxicity has been documented in the form of transient rises in liver transaminases.[226] A variety of symptoms attributable to halofantrine have included convulsions, cough, pruritus, skin rash, and acute intravascular haemolysis; all have been reported rarely.[227-231]

6.2 Severe Toxicity

The most serious toxicity is cardiac. Halofantrine has a quinidine-like effect on cardiac muscle that results in slower intracardiac conduction (increased PR and QRS intervals) and prolonged repolarisation (increased QTc interval); the latter is a well recognised predisposing factor for the development of ventricular arrhythmias.[232] It has been associated with sudden death. Cardiac toxicity is unpredictable because of the unpredictable absorption of halofantrine, which can be increased considerably by fatty food.[233] Significant QTc prolongation occurs at the standard and higher dosages (24 mg/kg/day for 3 days) and is directly correlated with halofantrine serum levels.[234-236] It is more likely to occur with mefloquine failures that are treated with high-dose halofantrine.[104] Over 20 sudden, unexpected fatalities have occurred.[237,238] First- and second-degree heart block have also been documented.[104,234] In a

clinical series of 42 halofantrine-treated Nigerian children aged between 1 and 11 years of age with uncomplicated falciparum malaria, two developed first-degree heart block and one developed Mobitz type I second-degree heart block. These ECG changes occurred within 48 hours, resolved after 72 hours, and were not associated with clinical symptoms.[239] Interestingly, desbutyl-halofantrine, the main metabolite, retains antimalarial activity but may lack the cardiotoxicity of halofantrine.[225]

6.3 Use in Pregnant and Breast-Feeding Women

Preclinical studies in rodents have demonstrated toxicity in terms of increased frequency of post-implantation embryonic death and reduced fetal bodyweight at dosages >15 mg/kg/day.[240] No teratogenic effects have been reported. Data in pregnant and breast-feeding women are lacking and, because of these limitations, halofantrine cannot be recommended in these groups.

6.4 Contraindications and Cautions

Halofantrine is potentially lethal and should not be given to patients with a prolonged QTc interval. Contraindications are: (i) halofantrine allergy; (ii) pre-existing cardiac disease (e.g. ischaemic heart disease, beriberi); (iii) congenital prolongation of the QTc interval (e.g. Romano-Ward syndrome); (iv) a family history of sudden unexpected death; (v) concomitant use of drugs that prolong the QTc interval (e.g. tricyclic antidepressants, phenothiazines, antihistamines, erythromycin); (vi) mefloquine treatment within the previous 3 weeks; (vii) pregnant and breast-feeding women; and (viii) children aged <1 year (because of a lack of data).

6.5 Role of Halofantrine

Clinical use is probably restricted to patients with drug-resistant falciparum malaria who have no pre-existing heart disease, are not on any drugs that can cause hypokalaemia and/or prolongation of the QTc interval, and for whom there are no better alternatives.[241] Although the baseline QTc interval appears not to correlate with subsequent halofantrine-induced QTc prolongation, some authorities still advise that the baseline QTc interval should be normal prior to initiating halofantrine.[241,242] The WHO does not recommend halofantrine as standby treatment for travellers.[47]

7. Atovaquone/Proguanil

Atovaquone/proguanil is a newly registered drug combination for malaria treatment and prophylaxis. Atovaquone is already used to treat *Pneumocystis carinii* pneumonia. Atovaquone/proguanil is active against the blood and developing liver forms of malaria.[243] The latter is a useful property that allows prophylaxis to start 1 day before entry into the endemic area and finish 1 week after leaving. Atovaquone/proguanil lacks hypnozoite activity; therefore, primaquine is required to achieve radical cure of vivax or ovale malaria.[244,245] Atovaquone/proguanil as treatment or prophylaxis is highly effective against drug-resistant *P. falciparum*.[246-251]

The dosage of atovaquone/proguanil treatment in adults is four tablets (each containing 250mg atovaquone/100mg proguanil) daily for 3 days, and one tablet daily as prophylaxis. Corresponding lower doses, using a paediatric formulation, are given for children, depending on their weight. There are no data available in children weighing <11kg. Atovaquone/proguanil absorption is increased by food and it should be taken with food or a milky drink.[252]

7.1 Mild and Moderate Adverse Effects

Atovaquone/proguanil is generally very well tolerated. Most adverse events that were reported in clinical trials were attributed to the malaria rather than the drug. Percentages of patients reporting symptoms varied widely, between 10% and 65%. Reported symptoms have included anorexia, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, and coughing. The tolerability of atovaquone/proguanil as treatment has been similar to that of other drugs. However, in one treatment trial of Thai adults, vomiting occurred in 14 (15.4%) of 91 atovaquone/proguanil recipients of whom 13 (14.3%) required retreatment; this compared with 2 of 91 mefloquine recipients, none of whom required retreatment ($p < 0.001$).[253] Vomiting was also a frequent symptom in Gabonese adults (33%) and adult travellers (44%) with falciparum malaria.[254,255] Overall, the rates of early vomiting (with-

in 1 hour) from pooled data were 8% in adults and 11% in children.[256] Vomiting after retreatment was low (<1%). Atovaquone/proguanil has been associated with elevation of liver function tests that have generally resolved within 28 days. Only a small number had raised liver function tests beyond this time. The greatest effect on liver function tests has been in European travellers, and adult Thai patients; the latter may have also been related to the high prevalence of hepatitis B. Overall, toxicity requiring treatment discontinuation is <1%.

The two prophylactic studies in travellers compared atovaquone/proguanil with chloroquine + proguanil[249] or mefloquine.[250] Overall, atovaquone/proguanil was better tolerated than either comparator regimen.[249,250] The majority of reported symptoms were of mild severity in both studies. Gastrointestinal symptoms (nausea, vomiting and abdominal pain) were reported by significantly more of the 511 chloroquine + proguanil recipients (20%) than of the 511 atovaquone/proguanil recipients (12%; $p < 0.05$).[249] Rates of mild/moderate neuropsychiatric adverse effects (headache, dizziness, abnormal dreams) were similar in both groups. One chloroquine + proguanil recipient had a convulsion. One atovaquone/proguanil recipient developed an 'allergic reaction' (details not given) that required withdrawal from the study. In the atovaquone/proguanil vs mefloquine study, rates of gastrointestinal symptoms were similar: 16% (n = 493) vs 19% (n = 483).[250] Mefloquine recipients had significantly higher rates of neuropsychiatric symptoms (strange vivid dreams, insomnia, dizziness/vertigo, anxiety and depression). For both groups, the majority of adverse effects were mild. Moderate (interfered with daily activity) or severe (medical advice sought) adverse effects that were considered drug related and resulted in drug discontinuation numbered six (1.2%) in the atovaquone/proguanil group and 24 (4.9%) in the mefloquine group ($p = 0.001$); 19 of the 24 withdrawals were because of neuropsychiatric events. In a randomised, placebo-controlled prophylaxis trial in Indonesian adults, atovaquone/proguanil was well tolerated. Four symptoms (stomatitis, abdominal pain, malaise, and back pain) were reported more frequently in the atovaquone/proguanil group than in the placebo group. The incidence densities of these four symptoms were low at <1.5 complaints per person-year.[257]

7.2 Severe Adverse Effects

Serious toxicity is rare. Anaphylaxis was reported in one patient during clinical trials.[256]

7.3 Use in Pregnant Women

The manufacturer states that animal studies revealed no teratogenic or embryotoxic effects.[258] There are currently only preliminary pharmacokinetic and efficacy data on the use of atovaquone/proguanil in pregnancy.[259] Atovaquone/proguanil cannot be recommended yet; however, it may be used if no other suitable antimalarial drug is available.

7.4 Use in Breast-Feeding Women

It is not known whether atovaquone is excreted into human milk. In a rat study, atovaquone concentrations in the milk were 30% of the concurrent atovaquone concentrations in the maternal plasma. Proguanil is excreted into human milk in small quantities. Caution should be exercised when atovaquone/proguanil is administered to nursing women.[258]

7.5 Contraindications and Cautions

Atovaquone/proguanil should not be used in those with known allergy or severe toxicity to either drug. Pregnancy is also a relative contraindication because of lack of safety data. Atovaquone/proguanil should not be used in patients (treatment) or travellers (prophylaxis) with severe renal disease (creatinine clearance <30 mL/min). Proguanil alone has caused megaloblastic bone marrow toxicity in renal failure patients.[260] There are no data on the use of atovaquone/proguanil in liver impairment.[258]

8. Amodiaquine

Amodiaquine is structurally similar and cross-resistant to chloroquine.[261,262] It is effective against low-level chloroquine-resistant *P. falciparum* but not against highly chloroquine-resistant parasites.[263-265] Amodiaquine had fallen out of favour because of its serious toxicity when used as prophy-

laxis. However, it is becoming increasingly recognised that amodiaquine is a useful drug for treating falciparum malaria in Africa. It is inexpensive, has good tolerability and lacks a bitter taste, an advantage for paediatric use.[266] The WHO recommended dosage is 10 mg/kg base once daily for 3 days.

8.1 Mild and Moderate Adverse Effects

The systematic collection of tolerability data on amodiaquine has been somewhat thin until recently. Amodiaquine alone or combined with oral artesunate for 3 days was used in 941 children with uncomplicated falciparum malaria.[267] Tolerability was good. Drug-related symptoms were reported by a small number of children, e.g. 11 (1.2%) had drug-induced vomiting necessitating alternative treatment, and 8 (0.9%) reported itching. No clinical or biochemical evidence of hepatic reactions were detected; indeed, liver function tests improved with disease resolution. There was a decline in the mean absolute neutrophil counts until day 21; thereafter, the mean count increased. By day 28, 9 of 153 children (6%) with paired day 0 to day 28 samples had developed neutrophil counts of <1000 mm^3. These children were afebrile, asymptomatic, and one had recurrent falciparum parasitaemia.[60] The natural history and clinical significance of neutropenia in these children remains unclear. There are no published studies of the possible cumulative toxicity of amodiaquine following repeated use. However, data from a trial in Nigerian children has not demonstrated serious hepatic or haematological reactions (P. Olumese, personal communication).

Data from other trials of amodiaquine in combination with sulfadoxine/pyrimethamine or artesunate also demonstrate good tolerability.[268,269] In the 3-arm amodiaquine vs sulfadoxine/pyrimethamine vs amodiaquine + sulfadoxine/pyrimethamine study, the total white cell counts were stable on day 14 but there was a decline in the mean neutrophil counts for all three groups.[269] In one study of healthy volunteers, one woman developed an asymptomatic rise in liver function tests following two sequential doses of artesunate (day 0), amodiaquine (day 7), and both drugs together on day 28.[270]

Case reports in the literature have documented rare neurological problems such as protruding tongue, intention tremor, excess salivation, and dysarthria in four African patients who were treated with amodiaquine.[271] In two patients, these signs occurred on re-exposure to amodiaquine. Yellow pigmentation of skin and mucosae, the development of corneal and conjunctival inclusion bodies, and retinopathy have been reported in one patient following amodiaquine use for 1 year.[272]

The tolerability data from these clinical trials are favourable but more studies are needed to document the effect of amodiaquine on the neutrophil count. More amodiaquine safety data will also need to be collected systematically on the use of repeat amodiaquine treatment.

8.2 Severe Adverse Effects

Amodiaquine has caused serious and, in some cases, fatal liver and bone marrow toxicity in European travellers when used as prophylaxis.[273-275] Agranulocytosis usually developed between 5 and 14 weeks of prophylaxis and was associated with hepatitis in some travellers. Based on UK data, the risk of developing agranulocytosis was estimated as 1 in 2000 to 2200, with a risk of death of 1 in 31 300, and 1 in 15 650 for a serious hepatic reaction.[65,273] Amodiaquine had been known to cause neutropenia on rare occasions when used for the treatment of rheumatoid arthritis but data from this era are limited.[276] The pathogenesis of amodiaquine-induced hepatitis is unclear but amodiaquine may exert a direct toxic effect on the liver through production of a quinine imino intermediate or may act via IgG anti-amodiaquine antibodies.[277,278] Hepatitis has occurred from as early as 3 weeks to as long as 10 months of amodiaquine prophylaxis. The clinical features of reported cases have ranged from a mild transient elevation of liver enzymes with few symptoms, to fulminant hepatitis resulting in slow recovery of liver function or death.[275]

8.3 Overdose Toxicity

Published data are scant. Amodiaquine appears to lack the serious cardiac toxicity of chloroquine.[35]

Table I. Recommended dosages for use of artemisinin derivatives

Type of malaria	Drug and dosage
Plasmodium falciparum	Oral artesunate monotherapy: 4 mg/kg on day 1 followed by 2 mg/kg/day for 6 days (total dose 16 mg/kg)
	Oral artesunate in combination: 4mg/kg/day for 3 days (see section 9.7)
Severe *P. falciparum* malaria	Intravenous artesunate: given daily, starting with 2.4 mg/kg on the first day followed by 1.2 mg/kg/day[a]
	Intramuscular artemether: 3.2 mg/kg on day 1, followed by 1.6 mg/kg/day[a]
P. vivax	The optimal dose has not yet been determined but in general this parasite is more sensitive. A total dose of artesunate of 10 mg/kg over 5 days rapidly cleared vivax parasitaemia and proved highly effective in Thai patients[282]

a Parenteral therapy may be followed by an oral artemisinin derivative to complete 7 days of therapy or by another effective antimalarial drug after at least 3 days of the parenteral artemisinin.

8.4 Use in Pregnant and Breast-Feeding Women

Published data are lacking. Amodiaquine cannot be recommended in breast-feeding women at this time.

8.5 Contraindications and Cautions

Amodiaquine must not be used as prophylaxis. Known allergy contraindicates the use of amodiaquine. Future use and the documentation of adverse effects will determine other possible contraindications.

9. Artemisinin Derivatives

The artemisinin derivatives include artesunate, artemisinin, dihydroartemisinin, artemether and arteether. In the early 1970s, Chinese scientists characterised the antimalarial properties of these agents and their excellent tolerability and safety.[279,280] Extensive experience now exists with their use in South East Asia over the past 15 years and more recent experience has been gained in Africa and Latin America.

Artemisinin derivatives are currently the most active antimalarial drugs and are given once daily.[281] Recommended dosages are given in table I.

9.1 Reported Adverse Effects

A review of published and unpublished studies of the artemisinin derivatives (n = 8844) has confirmed the earlier Chinese findings of excellent tolerability.[283] No serious adverse drug reactions were reported. Adverse events were independent of the artemisinin and the route of administration. Haematological changes, assessed in 4062 patients, were neutropenia (but not agranulocytosis) in 52 patients (1.3%), reduced reticulocyte count in 25 patients (0.6%), anaemia in eight patients (0.2%), and eosinophilia in 40 patients (1.0%). Acute haemolysis occurred in seven patients treated with artemether. An elevated aspartate aminotransferase occurred in 36/3893 patients (0.9%). ECG abnormalities without clinical effect were reported in <1.3% of 2638 patients: transient bradycardia (1.1%); prolongation of the QTc interval (1.2%); and very small numbers of patients with prolonged PR interval (1st degree atrioventricular block), atrial extrasystoles, and nonspecific T-wave changes.

Price et al. have conducted a detailed study of the tolerability of the artemisinin derivatives on the western border of Thailand.[284] In these prospective studies of uncomplicated falciparum malaria, the oral artemisinins were used either as monotherapy (artesunate [n = 630], artemether [n = 206]), or in combination with mefloquine (15 or 25 mg/kg) in 2826 patients. The artemisinin derivatives were associated with substantially fewer adverse effects than the mefloquine-containing regimens: acute nausea (16% vs 31%), vomiting (11% vs 24%), anorexia (34% vs 51%), and dizziness (15% vs 47%). Oral artesunate or artemether alone were very well tolerated. There was no difference in the incidence of possible adverse effects between the two drugs, and no evidence that either derivative caused allergic reactions, neurological or psychiatric reactions, or cardiovascular or dermatological toxicity. Acute intravascular haemolysis occurred in three patients treated with mefloquine and artesunate. Since these data were published, there have been

two cases of acute urticaria and anaphylaxis following oral artesunate alone.[285] In total, six patients have experienced these reactions out of a total of some 17 000, giving an estimated risk for developing an allergic reaction as 1 in 2833.[285]

9.2 On the Question of Neurotoxicity

Animal studies have documented CNS toxicity with artemisinin derivates, which has raised the question of whether neurotoxicity might occur in humans. Dogs that received high doses of intramuscular artemether or arteether developed a peculiar selective pattern of damage to the brain stem, in particular the reticular formation, the vestibular system nuclei, and nuclei related to the auditory system. Clinical features included gait disturbances, loss of spinal and pain response reflexes, and prominent loss of brain stem and eye reflexes, cardiorespiratory depression, and death. ECG changes included prolongation of QTc interval and bizarre ST-T segment changes.[286] A similar selective pattern of brain stem pathology was also found in mice, rats and Rhesus monkeys given arteether or artemether.[287,288] In mice, parenteral artemether was more neurotoxic than artesunate, resulting in escalating, irreversible neurological deficits (balance) and death with increasing doses.[289] Recent studies have shown that neurotoxicity is determined by the pharmacokinetic properties of the drugs. Sustained CNS exposure from slowly absorbed or eliminated artemisinins is considerably more neurotoxic than intermittent brief exposure. Thus intramuscular artemether and arteether are more neurotoxic in experimental animals than these drugs given orally, or to artesunate given by any route.

There has been one case report of a patient developing acute cerebellar dysfunction manifest by slurred speech, gait ataxia, impaired heel-shin movement and dysdiadochokinesis after treatment of falciparum malaria with oral artesunate.[290] The cause of these signs is unclear but may have been malaria related.[291] Detailed neurological data comes from Price et al.[284] Neurological examinations were conducted in children aged >5 years of age at baseline and on days 2, 7, and 28 post-treatment and included tests for: (i) co-ordination (heel-toe ataxia); (ii) fine finger dexterity (ability to pick up a paracetamol 500mg tablet); (iii) hearing (using a 256Hz tuning fork); (iv) nystagmus; and (v) balance (Romberg's test). Examinations were carried out in 1971 patients who received artemether (n = 307) or artesunate (n = 1664), either as monotherapy (n = 144) or combined with mefloquine (n = 1693). Neurological examinations were also conducted on 134 patients who received mefloquine alone.

On day 2, six of the 733 patients (0.8%) without neurological deficit on admission developed neurological signs: heel-toe ataxia (n = 1), positive Romberg's sign (n = 3), both signs (n = 2), nystagmus (n = 1) and impaired finger dexterity (n = 1). They received mefloquine + artemisinin derivatives (n = 1) or an artemisinin derivatives alone (n = 5). These signs were significantly associated with dizziness (RR = 6.2 [95% CI: 3.1–12]) and resolved within 1 week in all six patients. On day 7, six of 938 patients (0.6%) developed new heel-toe ataxia (n = 2), a positive Romberg's sign (n = 1), both signs (n = 2), nystagmus (n = 1), and dizziness, headache and weakness (n = 1). All had received mefloquine alone or in combination. All signs resolved.

There was no association between neurological symptoms and signs and type or dose of artemisinin derivative. No patient developed deafness, or permanent neurological abnormalities. These data show that short-course therapy with the artemisinins either alone or in combination with mefloquine was associated with self-limiting, minor neurological deficits in a minority of patients during the first few days of falciparum malaria.

Further neurological investigations (clinical neurological evaluation, audiometry, and early latency auditory-evoked responses) were done in a case-control study of 79 patients with falciparum malaria. These 79 patients had been treated with ≥2 courses of oral artemether or artesunate within the previous 3 years. They were age- and sex-matched with 79 controls living in the same area of northwest Thailand. There were no consistent differences in any of these test results between the cases and controls.[292] There was also no evidence of neurological abnormalities in a detailed evaluation of Vietnamese patients who had received multiple courses of artemisinin derivatives in whom and auditory evoked potentials were measured.[293]

These data provide no evidence that short course therapy with the artemisinins either alone, or in combination with mefloquine, are associated with neurotoxicity in man. They support the continued use and study of the artemisinin derivatives.[294,295]

9.3 Overdose Toxicity

There have not been any published reports of artemisinin overdose in patients.

9.4 Use in Pregnant Women

Published data on the artemisinin derivatives for treating malaria in pregnancy have come from China and the Thai-Burmese border.[296-301] A recent study of accidental exposure to artesunate and sulfadoxine/pyrimethamine in Gambian women in all three trimesters of pregnancy has added more useful data.[299] The Chinese data that are reported in English are brief and report the treatment of 23 women with artemether or artemisinin administered between 17 and 38 weeks of gestation. These studies found no evidence of fetal or maternal toxicity. Most of the experience with the artemisinins in pregnancy comes from Thailand. A recent publication summarises observational data from various trials. Artesunate (n = 528) or artemether (n = 11) was used to treat 539 episodes (461 women) of acute *P. falciparum* malaria, including 44 episodes in the first-trimester of pregnancy. The artemisinins were well tolerated with no evidence of adverse effects. Birth outcomes did not differ significantly to community rates for abortion, stillbirth, congenital abnormality, and mean gestation at delivery. All new borns who were followed up for 1 year, developed normally, including those who had been exposed to an artemisinin in the first trimester of pregnancy.[301] The Gambian study (n = 287) also failed to show any obstetric and fetal toxicity compared with women who had not been exposed to artesunate plus sulfadoxine/pyrimethamine.[299] These data are encouraging but more safety data for the artemisinin derivatives are needed.

There are no published data on the use of artesunate or artemether for severe malaria in pregnant women although they have been used widely and proved very effective. They have a significant advantage over quinine and quinidine in that they do not cause hypoglycaemia. Thus, these drugs are considered a good choice for the treatment of severe malaria in pregnancy because they are highly efficacious, better tolerated, and easier to administer than quinine.[169]

9.5 Use in Breast-Feeding Women

Published data on the use of the artemisinin derivatives in breast-feeding women are lacking but experience in Thailand has not shown any apparent infant toxicity (R. McGready, personal communication).

9.6 Contraindications and Cautions

Contraindications are few; namely, documented drug allergy. Because animal studies have shown embryonic death, artemisinin derivative use in the first trimester of pregnancy should be restricted to women with severe malaria or uncomplicated, multidrug-resistant *P. falciparum* for whom there is no safer alternative. The artemisinin derivatives may be used in the second and third trimesters of pregnancy in areas of drug resistance or where other drugs are less effective.

9.7 Combination Therapy

Combining an artemisinin derivative with current or new antimalarial drugs is becoming increasingly accepted as the therapeutic way forward for malaria-endemic countries.[302] Extensive use of artesunate combined with mefloquine on the Thai-Burmese border has produced consistently high cure rates (>95%) for uncomplicated malaria, and reduced the transmission of *P. falciparum*.[98] The toxicity of artesunate plus mefloquine is the same as mefloquine monotherapy. This has also been found with artesunate in combination with either sulfadoxine/pyrimethamine or amodiaquine.[267,303,304] There are several other artesunate combination studies that have been conducted and more safety data will be published in the near future.[305]

10. Artemether/Lumefantrine

Artemether/lumefantrine is a fixed-dose combination of artemether and lumefantrine, a compound structurally similar to quinine, mefloquine, and halofantrine. Artemether/lumefantrine has high effi-

cacy against falciparum and vivax malaria but has no antihypnozoite activity.

Cure rates of *P. falciparum* with the original four-dose regimen have generally been high in young African children (87–93%) and Indian adults (95%).[306-309] However, cure rates were inadequate for treating falciparum malaria in travellers (82%) and on the Thai-Burmese border (70–85%).[108,109,310] The six-dose regimen produced high (>95%) efficacy rates in Thailand,[311] and is now generally accepted as the optimum dose everywhere.

10.1 Mild and Moderate Adverse Effects

Experience with artemether/lumefantrine is increasing rapidly. In large scale clinical trials artemether/lumefantrine was very well tolerated whether used as four or six doses. Artemether/lumefantrine has been shown to have better tolerability than either mefloquine alone or artesunate plus mefloquine.[108,109] Reported adverse effects have generally been mild and have included gastrointestinal upset (anorexia, nausea, vomiting, abdominal pain and diarrhoea), headache, dizziness, fatigue, sleep disturbance, palpitations, myalgia, arthralgia (all of which could be disease related), and rash.[312] Because it has a similar structure to mefloquine, halofantrine, and quinine, it might be expected that cardiotoxicity would be a problem. However, detailed prospective studies have not demonstrated any cardiotoxicity. In healthy human volunteers and patients, there were no clinically significant changes in the QTc interval and there was no correlation between the QTc intervals and plasma lumefantrine concentrations.[313,314] Furthermore, in the volunteers, there was no clinically relevant difference in the QTc intervals comparing mefloquine or artemether/lumefantrine alone and when given together.

10.2 Severe Adverse Effects

According to the manufacturer, there were 20 reported serious adverse in 1869 patients. Nineteen of these adverse events could be explained on the basis of the malarial episode or represented concurrent illnesses (including severe anaemia in children, unsatisfactory response, pneumonia, hepatitis). Artemether/lumefantrine may have contributed to only one of the reported serious adverse events – the development of haemolytic anaemia in a 35-year-old patient after the drug had been discontinued for 13 days.[312]

10.3 Use in Pregnant and Breast-Feeding Women

There are no published data on the use of artemether/lumefantrine in pregnant or breast-feeding women. More studies are needed. Until data become available, clinicians should only use artemether/lumefantrine for treating drug-resistant falciparum malaria if no other suitable drugs are available.

10.4 Contraindications and Cautions

Artemether/lumefantrine should not be used in patients with known allergy to either component. Until more data become available, artemether/lumefantrine lumefantrine is not recommended for very young children although there is no reason to suspect there would be any specific problems in infants. It should also not be used in patients with renal and/or hepatic disease. Artemether/lumefantrine may be used in pregnant and breast-feeding women if no other suitable drugs are available given that it is highly effective against multidrug-resistant *P. falciparum*. Clinicians should ideally follow-up such women to ascertain the outcome of pregnancy and the effects on the breast-fed infant.

11. Primaquine

Primaquine is an 8-aminoquinoline that was introduced over 50 years ago. It has broad but variable antimalarial activity. Its principal action is against liver schizonts (causal activity), liver hypnozoites, and gametocytes; there is weak activity against asexual forms of *P. vivax*, *P. malariae*, and *P. ovale*.[315,316]

Primaquine is used primarily to achieve radical cure (complete elimination) of the two relapsing malarias, *P. vivax* and *P. ovale*.[317] Because the sensitivity of *P. vivax* hypnozoites varies, the optimal regimen against 'resistant' or 'tolerant' stains has been subject to much debate. In general, tropical vivax (e.g. Chesson strain from New Guinea) re-

quires a higher primaquine dosage (30 mg/day) than temperate vivax (15 mg/day). Standard treatment is 14 days but 21 days or retreatment is sometimes necessary; 5-day regimens are insufficient. Several publications have dealt with this issue in detail.[318-321]

11.1 Mild and Moderate Adverse Effects

Primaquine is generally well tolerated when used for radical cure, for the eradication of gametocytes (e.g. adult dose of 45mg base stat), and as daily prophylaxis (30mg base daily adult dose – taken with food).

11.1.1 Gastrointestinal Adverse Effects

Gastrointestinal toxicity is dose related and improved by taking primaquine with food.[322] Abdominal pain and/or cramps are commonly reported when taken on an empty stomach. Primaquine at a dosage of 15 mg/day resulted in mild abdominal pain in 3% of American Caucasian individuals, a rate similar to placebo. This increased with an increase in dosage to 12% (22.5 mg/day), 10% (30 mg/day), including 3% who developed epigastric distress necessitating the administration of antacids, 71% (60 mg/day), and 100% (120 mg/day). These higher doses also caused nausea, cramping abdominal pain, and occasional vomiting. Mild diarrhoea has also been reported occasionally.[10]

11.1.2 Changes in White Cell Count

Increased and decreased white cell counts have been associated with primaquine. Leucocytosis is probably a result of bone marrow stimulation and was reported in 4–21% of primaquine recipients at dosages of 15–60 mg/day. Leucopenia was reported in 4 of 43 recipients of high-dosage primaquine (120 mg/day).[322] Co-administration with other myelotoxic drugs (e.g. sulphonamides), or administration to patients with diseases complicated by myelosuppression may increase the risk of leucopenia.[323] Brennecke et al. found an increased risk of granulocytopenia when primaquine was given to patients with rheumatoid arthritis.[324]

11.1.3 Development of Methaemoglobinaemia

Primaquine is oxidant and converts haemoglobin (Hb) to methaemoglobin (metHb), an action which is dose dependent.[322] Cyanosis may be evident clinically when the metHb concentration exceeds 15–20 g/L (around 10% of the normal level of haemoglobin). Cyanosis is a rare finding – only one case was found in 3000 American soldiers receiving 15 mg/day for 14 days.[325] MetHb levels of up to 25% are usually well tolerated. With daily primaquine administration, the mean metHb level rises but there is wide interindividual variation. MetHb levels exceeding 10% with primaquine dosages of 15 or 22.5 mg/day are unusual; levels of 16–18% were found in three of 46 (6.5%) Australian soldiers.[326] Cohen et al. described six American soldiers (including one pair of twins) who developed cyanosis following weekly prophylaxis with chloroquine (300mg), primaquine (45mg), and dapsone (25mg).[327] Their measured metHb levels were 20–32%. All had nicotinamide adenine dinucleotide (NADH) metHb reductase deficiency, an autosomal recessive disorder. *In vitro* work showed that all three drugs had the potential to produce metHb in red cells taken from these subjects. The authors concluded that this drug combination probably had an additive effect in producing cyanosis, a similar finding to a later study examining primaquine and chloroquine.[327,328] Stopping primaquine results in resolution of symptoms and signs within a few days. Methylthioninium chloride (methylene blue) is an antidote. MetHb is generally less pronounced in people with G6PD deficiency because the older red cells, which are more prone to developing metHb, have usually haemolysed.

11.2 Haemolysis

Acute haemolysis is a well recognised side effect of primaquine in individuals with G6PD deficiency, other enzyme deficiencies (e.g. glutathione synthase) that counter oxidant stress, and several haemoglobinopathies (e.g. Hb Zurich, Hb Torino).[329] Although first recognised in the 1920s with pamaquine, it was not until the early 1950s and the development of primaquine that haemolysis was noted as a significant problem amongst American soldiers of African descent. At that time, the cause of haemolysis was unknown and was labelled 'primaquine sensitivity'.[330] Subsequently, this led to the discovery of the sex-linked G6PD deficiency. The two common forms of G6PD deficiency are the African (A-) and Mediterranean forms; the former

has a higher level (10–60%) of enzyme activity compared to the latter (<10%). Other G6PD variants (e.g. Asian variants) generally fall into these two categories. Haemolysis has three phases: acute haemolytic, recovery, and equilibrium.[323] The severity of haemolysis is related to the degree of G6PD deficiency and the dose of primaquine, and may be exacerbated by concurrent infections, liver disease (reduced primaquine metabolism), renal impairment (delayed primaquine excretion), and the co-administration of other drugs with haemolytic potential, e.g. sulphonamides.[323,331,332]

11.2.1 Haemolysis in the African Variant (A^-) G6PD Deficiency

Work in the 1950s, using 30mg of primaquine base administered daily to 110 African Americans, found that haemolysis usually appeared on the second or third day of drug administration and continued for a further 5–7 days.[323,333] As Hb levels fell, there was an increase in unconjugated bilirubin, haemogloginuria, and reticulocytosis. Heinz bodies appeared early on but disappeared as the haemolysis worsened. Haemolysis ceased within 4 days of discontinuing primaquine. With continued primaquine administration, anaemia (mean 10 g/dL) reached its nadir on day 10. Hb recovered slowly over 4 weeks to reach normal levels. The latter were maintained despite continuing primaquine administration because continuing haemolysis of the oldest erythrocytes was compensated for by increased haematopoiesis. Of the 110 individuals thus treated, 17 developed mild anaemia with a mean fall of Hb of 1.8 g/dL from baseline. However, five subjects developed anaemia of between 9–10 g/dL after between 4–9 days of primaquine. In another cohort of 50 African Americans, daily administered primaquine (15mg base) resulted in mild anaemia in 12; the mean drop in Hb was 2 g/dL. Primaquine base at a dose of 15mg for 14 days can be given to these patients without individual monitoring because the haemolysis is mild and self-limiting. If higher doses are required e.g. 30mg daily (14 days) to treat the Chesson strain of *P. vivax*, then monitoring is required because of the risk of severe, acute haemolysis.

11.2.2 Haemolysis in the Mediterranean Variant G6PD Deficiency

Individuals with these forms of G6PD deficiency have low enzyme levels in old and young red cells and are prone to develop severe anaemia. Primaquine base, at doses of 15 mg/day or 45 mg/week, has produced severe haemolysis, progressive haemoglobinaemia, haemoglobinuria, acute renal failure, and death.[334,335] In a study of Thai patients with vivax malaria (n = 13), who were given primaquine daily (15mg base) after standard dose chloroquine, haemolysis occurred in all 13. The degree of haemolysis, graded only as <20% vs >20% haemolysis, was not related to primaquine pharmacokinetics, which were similar between the two groups and to 13 control subjects without G6PD deficiency.[336] In Sri Lanka, a hospital based study of primaquine induced haemolysis in 21 children with partial or gross G6PD deficiency, was associated significant morbidity and a CFR of 19% (4/21). On admission, nine children had congestive cardiac failure, five acute renal failure, and 14 required blood transfusion. Two children who died had also been given aspirin, a known haemolytic drug in G6PD deficiency. Half of the 21 children had been given higher than the recommended doses of primaquine, emphasising the potential severe toxicity of primaquine in such patients.[337]

11.3 Tolerability of Weekly Administration

Alving et al. studied weekly administration of primaquine (45mg or 60mg for 8 weeks) for experimentally-induced vivax malaria in African Americans. Both regimens were well tolerated and resulted in little haemolysis. In addition, the rate of radical cure was higher than rates using daily primaquine (15mg for 14 days), and weekly primaquine (30, 45, and 60mg) administered over 4 weeks.[338]

In Korea, weekly chloroquine (300mg) and primaquine (45mg), were administered as prophylaxis to approximately 50 000 American soldiers over 22 weeks, and 139 Turkish soldiers over 14 weeks.[339] There were no reports of acute haemolysis in the Americans; a small number reported intestinal cramps, and loose bowel movements several hours after drug administration. Similarly, no haemolysis was reported in the Turkish soldiers but of 104 blood samples taken, only one soldier was

G6PD deficient. In Thailand, the haemolytic potential of primaquine 45mg was investigated in seven volunteers with G6PD deficiency, two of whom also had Hb E trait. Five developed haemolysis that lasted for 2–3 days.[340] The 45mg weekly regimen for 6 weeks is now recommended for radical cure of vivax or ovale malaria in patients with the African or other variants of mild G6PD deficiency.

11.4 Tolerability of Prophylaxis

Primaquine is being developed as a daily prophylactic drug. Six published studies have assessed primaquine as prophylaxis in Indonesia (30mg daily or on alternate days), Colombia (30mg daily ± chloroquine), and Kenya (15mg daily in children). Prophylactic efficacies were high against falciparum (74–95%) and vivax malaria (85–92%).[341-345] In the Kenyan children, aged 9–14 years, 15mg daily had a prophylactic efficacy of 85% against falciparum parasitaemia and 91% against clinical disease.[346] G6PD-deficient subjects were excluded from these studies. Primaquine was generally well tolerated by all subjects, a substantial number of whom were young, healthy soldiers or adult males. No serious adverse events were reported.

In the Kenyan children, primaquine (n = 32) and placebo recipients (n = 34) reported similar symptoms over 11 weeks. In Papua, Indonesia, the rate of symptom complaints (any symptom) that was reported weekly by Javanese men over 52 weeks of prophylaxis was higher in the primaquine group (30 mg/day) compared with placebo: 4.7/100 vs 3.6/100 person-weeks (p = 0.01).[341] Analysis of weekly reported symptoms showed that of 16 specific and common symptoms (e.g. fever, gastrointestinal symptoms, headache, etc.), only cough was significantly higher in the primaquine arm. During the study, six of 22 men (27.3%) reported abdominal discomfort when primaquine was taken on an empty stomach. Routine haematology and biochemistry were normal in the primaquine recipients at study end but mean levels of methaemoglobinaemia were significantly higher in the primaquine arm (5.8% [range 1.4–13%]) compared with the placebo (0.7% [0–3%]) and chloroquine (0.7% [0–3%]) arms. These levels were not associated with respiratory symptoms or cyanosis. One week after primaquine was stopped, mean metHb levels fell significantly to 2.4% (range 0–4.5%). Comparable findings were demonstrated in another placebo-controlled trial of 97 adults and children.[342]

Low rates of gastrointestinal symptoms (nausea, vomiting, abdominal pain and diarrhoea) have been reported when primaquine was administered with food. In people in Papua, this was 0.4/0.4 per person-year (five complaints over 677 person-weeks).[343] In Colombian soldiers, 5–6% reported gastrointestinal symptoms and 2–2.5% discontinued primaquine; the soldiers took their primaquine with a light breakfast (coffee, bread, and occasionally an egg).[344,345]

11.5 Overdose Toxicity

Experience with primaquine overdose is limited. Gastrointestinal symptoms, haemolysis, methaemoglobinaemia, and cyanosis are important features. Treatment includes gastric lavage, activated charcoal, oxygen, and methylthioninium chloride.[35] There has been a small case series of five HIV-positive cases of methaemoglobinaemia caused by either primaquine or dapsone or the combination of the two. Two cases resulted from intentional overdoses of dapsone, and three developed within several days of commencing primaquine while dapsone remained present in the bloodstream. Four required intravenous methylthioninium chloride, oxygen, and blood transfusions while the one mild case responded to oxygen and drug discontinuation.[347]

11.6 Use in Pregnant and Breast-Feeding Women

Primaquine is contraindicated during pregnancy because of the possibility of inducing haemolysis and methaemoglobinaemia in the fetus. Pregnant women who require radical treatment for vivax malaria should receive primaquine after delivery. There are no data on primaquine excretion into breast milk.

11.7 Contraindications and Cautions

Primaquine is contraindicated in: (i) patients with severe forms (non-African) of G6PD deficiency; (ii) pregnancy; and (iii) neonates.[348] The lower age limit of safety for children has not been established. One recommendation is to avoid primaquine in children aged <1 year, the other is <4 years of

age.[312,349] Primaquine should be administered after clinical resolution of malaria to avoid possible early, drug-induced vomiting, haemolysis, and myelosuppression. Because primaquine may produce leucopenia, caution is necessary if used in patients with systemic diseases that are associated with neutropenia, e.g. rheumatoid arthritis, systemic lupus erythematosus.

12. Antimalarial Drugs in Development

There are several drugs in various stages of development that may well have a role in malaria control and treatment. These include chlorproguanil/dapsone alone and combined with artesunate, pyronaridine, tafenoquine, and bulaquine. A fixed-dose combination of dihydroartemisinin and piperaquine has been developed but there is no experience of this drug outside of East Asia. Assessment of the tolerability of these drugs is ongoing and will be the subject of a future review.

Acknowledgements

Neither author has a conflict of interest. This review was undertaken without any funding support. Nicholas J. White is a Wellcome Trust Principal Fellow and works with the Wellcome Trust-Mahidol University-Oxford Tropical Medicine Research Programme.

The views expressed in this review represent those of the authors and not of their institutions.

References

1. WHO. World malaria situation in 1994. Wkly Epidemiol Rec 1997; 72: 269-76
2. Snow RN, Craig M, Deichmann U, et al. Estimating mortality, morbidity and disability due to malaria among Africa's non-pregnant population. Bull World Health Organ 1999; 77: 624-40
3. Bossuyt PMM. Better standards for better reporting of RCTs: a revised CONSORT statement should further improve standards of reporting. BMJ 2001; 322: 1317-8
4. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356: 1255-9
5. Nosten F, ter Kuile F, Maelankirri L, et al. Malaria during pregnancy in an area of unstable endemicity. Trans R Soc Trop Med Hyg 1991; 85: 424-9
6. Ahmed Y, Mwaba P, Chintu C, et al. A study of maternal mortality at the University Teaching Hospital, Lusaka, Zambia: the emergence of tuberculosis as a major non-obstetric cause of maternal death. Int J Tuberc Lung Dis 1999; 3: 675-80
7. Krogstad DJ. Malaria as a re-emerging disease. Epidemiol Rev 1996; 18 (1): 77-89
8. Fox W. Self-administration of medicaments: a review of published work and a study of the problems. Bull Int Union Tuberc 1962; 32: 307-31
9. White NJ, Nosten F, Looareesuwan S, et al. Averting a malaria disaster. Lancet 1999; 353: 1965-7
10. Martindale Pharmacopoeia. Royal Pharmaceutical Society of Great Britain. 32nd edition. In: Parfitt K, editor. London; Pharmaceutical Press, 1999: 426-30
11. Mnyika KS, Kihamia CM. Chloroquine-induced pruritus: its impact on chloroquine utilization in malaria control in Dar es Salaam. J Trop Med Hyg 1991; 94: 27-31
12. Sowunmi A, Walker O, Salako LA. Pruritus and antimalarial drugs in Africans. Lancet 1989; II: 213
13. Bussaratid V, Walsh DS, Wilairatana P, et al. Frequency of pruritus in Plasmodium vivax malaria patients treated with chloroquine in Thailand. Trop Doct 2000; 30: 211-4
14. Wolf R, Ruocco V. Triggered psoriasis. Adv Exp Med Biol 1999; 455: 221-5
15. Olsen TG. Chloroquine and psoriasis. Ann Intern Med 1981; 94: 546-7
16. Wilairatana P, Looareesuwan S, Riganti M, et al. Pustular eruption in a malaria patient treated with chloroquine. Int J Dermatol 1997; 36: 634-5
17. Millard TP, Smith HR, Lack MM, et al. Bullous pemphigoid developing during systemic therapy with chloroquine. Clin Exp Dermatol 1999; 24: 263-5
18. Stemberger H, Leimer R, Wiedermann G. Tolerability of long-term prophylaxis with Fansidar: a randomized double blind study in Nigeria. Acta Trop 1984; 41: 391-9
19. Tanenbaum L, Tuffanelli DL. Antimalarial agents. Arch Dermatol 1980; 116: 587-91
20. Fogh S, Schapira A, Bygbjerg IC, et al. Malaria prophylaxis in travellers to east Africa: a comparative prospective study of chloroquine plus proguanil with chloroquine plus sulfadoxine-pyrimethamine. BMJ 1988; 296: 820-2
21. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting east Africa. Lancet 1993; 341: 1299-303
22. Barrett PJ, Emmins PD, Clarke PD, et al. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone surveys of travellers. BMJ 1996; 313: 525-8
23. Durrheim DN, Gammon S, Waner S, et al. Antimalarial prophylaxis: use and adverse events in visitors to the Kruger National Park. S Afr Med J 1999; 89: 170-5
24. Carme B, Peguet C, Nevez G. Compliance with and tolerance of mefloquine and chloroquine + proguanil malaria chemoprophylaxis in French short-term travellers to sub-Saharan Africa. Trop Med Int Health 1997; 2: 953-6
25. Drysdale SF, Phillips-Howard PA, Behrens RH. Proguanil, chloroquine, and mouth ulcers [letter]. Lancet 1990; 335: 164
26. Hoebe C, de Munter J, Thijs C. Adverse effects and compliance with mefloquine or proguanil antimalarial chemoprophylaxis. Eur J Clin Pharmacol 1997; 52: 269-75
27. Avina-Zubieta JA, Johnson ES, Suarez-Almazor ME, et al. Incidence of myopathy in patients treated with antimalarials: a report of three cases and a review of the literature. Br J Rheumatol 1995; 34: 166-70
28. Boffa MJ, Chalmers RJG. Toxic epidermal necrolysis due to chloroquine phosphate. Br J Dermatol 1994; 131: 444-5
29. Bamber MG, Elder AT, Gray JA, et al. Fatal Stevens-Johnson syndrome associated with Fansidar and chloroquine. J Infect 1986; 13: 31-3
30. Nagaratnam N, Chetiyawardana AD, Rajiyah S. Aplasia and leukaemia following chloroquine therapy. Postgrad Med J 1978; 54: 108-12
31. Silman A, Shipley M. Ophthalmological monitoring for hydroxychloroquine toxicity: a scientific review of available data. Br J Rheumatol 1997; 36: 599-601

32. Rynes RI. Antimalarial drugs in the treatment of rheumatological diseases. Br J Rheumatol 1997; 36: 799-805
33. WHO. Practical chemotherapy of malaria: report of a WHO Scientific Group. World Health Organ Tech Rep Ser 1990; 805: 1-141
34. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. BMJ 1988; 297: 526-7
35. Jaeger A, Sauder P, Kopferschmitt J, et al. Clinical features and management of poisoning due to antimalarial drugs. Med Toxicol Adverse Drug Exp 1987; 2: 242-73
36. Riou B, Barriot P, Rimailho A, et al. Treatment of severe chloroquine poisoning. N Engl J Med 1988; 318: 1-6
37. White NJ, Miller KD, Churchill FC, et al. Chloroquine treatment of severe malaria in children: pharmacokinetics, toxicity, and new dosage recommendations. N Engl J Med 1988; 319: 1493-500
38. Garner P, Brabin B. A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas. Bull WHO 1994; 72: 89-99
39. Phillips-Howard PA, Wood D. The safety of antimalarial drugs in pregnancy. Drug Saf 1996; 14 (3): 131-45
40. Wolfe M, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. BMJ 1985; 290: 1466-7
41. Steketee RW, Wirima JJ, Slutsker L, et al. Malaria treatment and prevention in pregnancy: indications for use and adverse events associated with use of chloroquine or mefloquine. Am J Trop Med Hyg 1996; 55 (1 Suppl.): 50-6
42. Klinger G, Morad M, Westall CA, et al. Ocular toxicity and antenatal exposure to chloroquine or hydroxychloroquine for rheumatic diseases. Lancet 2001; 385: 813-4
43. Motta M, Tincani A, Faden D, et al. Antimalarial agents in pregnancy. Lancet 2002; 359: 524-5
44. Ogunbona FA, Onyeji CO, Bolaji OO, et al. Excretion of chloroquine and desethylchloroquine in human milk. Br J Pharmacol 1987; 23: 473-6
45. Edstein MD, Veenendaal JR, Newman K, et al. Excretion of chloroquine, dapsone and pyrimethamine in human milk. Br J Clin Pharmacol 1986; 22: 733-5
46. British National Formulary. British Medical Association and Royal Pharmaceutical Society of Great Britain (London). 2003 Mar; 45: 312-21
47. World Health Organisation. International travel and health. Geneva: WHO, 2002
48. Salako L, Walker O, Iyun AO. Pharmacokinetics of chloroquine in renal insufficiency. Afr J Med Med Sci 1984; 13: 177-82
49. Bradley DJ, Bannister B. Guidelines for malaria prevention in travellers from the United Kingdom for 2001. Commun Dis Public Health 2001; 4: 84-101
50. Cardiff Porphyria Service [online]. Available from URL: www.uwcm.ac.uk [Accessed 2003 Jan]
51. Sarkany RPE. The management of porphyria cutanea tarda. Clin Exp Dermatol 2001; 26: 225-32
52. Thornsvard CT, Guider BA, Kimball DB. An unusual reaction to chloroquine-primaquine. JAMA 1976; 235: 1719-20
53. Gladman DD, Blake R, Brubacher B, et al. Chloroquine therapy in psoriatic arthritis. J Rheumatol 1992; 19: 1724-6
54. Damstra RJ, van Vloten WA. Exacerbation of psoriasis caused by malaria prophylaxis with chloroquine and proguanil. Ned Tijdschr Geneeskd 1991; 135: 671-3
55. Luzar MJ. Hydroxychloroquine in psoriatic arthropathy: exacerbations of psoriatic skin lesions. J Rheumatol 1982; 9: 462-4
56. Looareesuwan S, Harinasuta T, Chongsuphajaisiddhi T. Drug resistant malaria, with special reference to Thailand. Southeast Asian J Trop Med Public Health 1992; 23: 621-34
57. Tierney LM, McPhee SJ, Papadakis MA, editors. Current medical diagnosis and treatment. New York (NY): McGraw Hill, 2000: 1504
58. Ekue JMK, Phiri DED, Sheth UK, et al. A double-blind trial of a fixed combination of mefloquine plus sulfadoxine-pyrimethamine compared with sulfadoxine-pyrimethamine alone in symptomatic falciparum malaria. Bull WHO 1987; 65: 369-73
59. Tjitra E, Suprianto S, Currie BJ, et al. Therapy of uncomplicated falciparum malaria: a randomized trial comparing artesunate plus sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine alone in Irian Jaya, Indonesia. Am J Trop Med Hyg 2001; 65: 309-17
60. Tropical Disease Research [TDR]. (Data on file)
61. Miller KD, Lobel HO, Satriale RF, et al. Severe cutaneous reactions among American travellers using pyrimethamine-sulfadoxine (Fansidar®) for malaria prophylaxis. Am J Trop Med Hyg 1986; 35: 451-8
62. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine-pyrimethamine in Switzerland [letter]. Lancet 1986; I: 610
63. Olsen VV, Loft S, Christensen KD. Serious reactions during malaria prophylaxis with pyrimethamine-sulfadoxine [letter]. Lancet 1982; II: 994
64. US Department of Health and Human Services. Adverse reactions to Fansidar and updated recommendations for its use in the prevention of malaria. JAMA 1985;253: 483
65. Phillips-Howard PA, West L. Serious adverse drug reactions to pyrimethamine-sulphadoxine, pyrimethamine-dapsone and to amodiaquine in Britain. J R Soc Med 1990; 83: 82-5
66. Hellgren U, Rombo L, Berg B, et al. Adverse reactions to sulfadoxine-pyrimethamine in Swedish travellers: implications for prophylaxis [letter]. BMJ 1988; 297: 1267
67. Hernborg A. Stevens-Johnson syndrome after mass prophylaxis with sulfadoxine for cholera in Mozambique. Lancet 1985; II: 1072-3
68. Bergoend H, Loffler A, Amar R, et al. Reactions cutanees survenues au cours de la prophylaxie de masse de la meningite cerebro-spinale par un sulfamide long-retard (propos de 997 cas). Ann Dermatol Venereol 1968; 95: 481-90
69. Taylor GM. Stevens-Johnson syndrome following the use of an ultra-long-acting sulphonamide. S Afr Med J 1968; 42: 501-3
70. Phillips-Howard PA, Behrens RH, Dunlop J. Stevens-Johnson syndrome due to pyrimethamine/sulfadoxine during presumptive self-therapy of malaria. Lancet 1989; II: 803-4
71. Langtry JAA, Harper JI, Staughton RCD, et al. Erythroderma resembling Sezary syndrome after treatment with Fansidar and chloroquine. BMJ 1986; 292: 1107-8
72. Lazar HO, Murphy RL, Phair JP. Fansidar and hepatic granulomas [letter]. Ann Intern Med 1985; 102: 722
73. Wejstal R, Lindberg J, Malmvall B-E, et al. Liver damage associated with Fansidar. Lancet 1986; I: 854-5
74. Tonder M, Nordy A, Elgjo K. Sulfonamide-induced chronic liver disease. Scand J Gastroenterol 1974; 9: 93-6
75. Zitelli BJ, Alexander J, Taylor S, et al. Fatal hepatic necrosis due to pyrimethamine-sulfadoxine (Fansidar). Ann Intern Med 1987; 106: 393-5
76. Selby CD, Ladusans EJ, Smith PG. Fatal multisystemic toxicity associated with prophylaxis with pyrimethamine and sulfadoxine (Fansidar). BMJ 1985; 290: 113-4
77. Svanbom M, Rombo L, Gustafsson L. Unusual pulmonary reaction during short term prophylaxis with pyrimethamine-sulfadoxine (Fansidar) [short report]. BMJ 1984; 288: 1876
78. McCormack D, Morgan WKC. Fansidar hypersensitivity pneumonitis. Br J Dis Chest 1987; 81: 194-6
79. Hitchings GH. Daraprim as an antagonist of folic and folinic acids. Trans R Soc Trop Med Hyg 1952; 46: 467

80. Chute JP, Decker CF, Cotelingam J. Severe megaloblastic anemia complicating pyrimethamine therapy. Ann Intern Med 1995; 122: 884-5
81. Wickramasihghe SN, Litwinczuk RAC. Effects of low concentrations of pyrimethamine on human bone marrow cells *in vitro*: possible implications for malaria prophylaxis. J Trop Med Hyg 1981; 84: 233-8
82. Bjorkman A, Phillips-Howard PA. Adverse reactions to sulfa drugs: implications for malaria chemotherapy. Bull World Health Organ 1991; 69: 297-304
83. Lindberg A, Bergqvist Y, Rombo L. Accidental overdose of pyrimethamine and sulphadoxine for malaria prophylaxis without adverse effects. Eur J Clin Pharmacol 1986; 31: 253-4
84. Burgmann H, Winkler S, Uhl F, et al. Mefloquine and sulfadoxine/pyrimethamine overdose in malaria tropica. Wien Klin Wochenschr 1993; 105: 61-3
85. Shulman CE, Dorman EK, Cutts F, et al. Intermittent sulphadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. Lancet 1999; 353: 632-6
86. Verhoeff FH, Brabin BJ, Chimsuku L, et al. An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birthweight in rural Malawi. Ann Trop Med Parasitol 1998; 92: 141-50
87. Schultz LJ, Steketee RW, Macheso A, et al. The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental *Plasmodium falciparum* infection among pregnant women in Malawi. Am J Trop Med Hyg 1994; 51: 515-22
88. Verhoeff FH, Brabin BJ, Hart CA, et al. Increased prevalence of malaria in HIV-infected pregnant women and its implications for malaria control. Trop Med Int Health 1999; 4: 5-12
89. Parise ME, Ayisi JG, Nahlen BL, et al. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. Am J Trop Med Hyg 1998; 59: 813-22
90. Notarianni LJ. Plasma protein binding of drugs in pregnancy and in neonates. Clin Pharmacokinet 1990; 18 (1): 20-36
91. Izumi H, Kokue E, Hayama T. The critical period of pyrimethamine teratogenesis in the rat. Nippon Juigaku Zasshi 1984; 46: 217-8
92. Harpey JP, Darbois Y, Lefebrve G. Teratogenicity of pyrimethamine [letter]. Lancet 1983; 399: 2
93. Pyrimethamine combinations in pregnancy. Lancet 1983 Oct; 29: 1005-7
94. Phillips-Howard PA, Steffen R, Kerr L, et al. Safety of mefloquine and other antimalarial agents in the first trimester of pregnancy. J Travel Med 1998; 5: 121-6
95. Hohlfeld P, Daffos F, Thulliez P, et al. Fetal toxoplasmosis: outcome of pregnancy and infant follow-up after in utero treatment. J Pediatr 1989; 115: 765-9
96. International Standard Prescribing Information. Roche, May 1997
97. Bang AT, Bang RA, Baitule SB, et al. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. Lancet 1999; 354: 1955-61
98. Nosten F, van Vugt M, Price R, et al. Effects of artesunate-mefloquine combination on incidence of *Plasmodium falciparum* malaria and mefloquine resistance in western Thailand: a prospective study. Lancet 2000; 356: 297-302
99. Cerutti C, Durlacher RR, de Alencar FE, et al. In vivo efficacy of mefloquine for the treatment of falciparum malaria in Brazil. J Infect Dis 1999; 180: 2077-80
100. Mockenhaupt FP. Mefloquine resistance in *Plasmodium falciparum*. Parasitol Today 1995; 11: 248-53
101. Lobel HO, Varma JK, Miani M, et al. Monitoring for mefloquine-resistant *Plasmodium falciparum* in Africa: implications for travellers' health. Am J Trop Med Hyg 1998; 59: 129-32
102. Ohrt C, Richie TL, Widjaja H, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1997; 126: 963-72
103. Lobel HO, Miani M, Eng T, et al. Long-term malaria prophylaxis with weekly mefloquine. Lancet 1993; 341: 848-51
104. Nosten F, ter Kuile FO, Luxemburger C, et al. Cardiac effects of antimalarial treatment with halofantrine. Lancet 1993; 341: 1054-6
105. Nosten F, Price RN. New antimalarials: a risk-benefit analysis. Drug Saf 1995; 12 (4): 264-73
106. Kofi Ekue JM, Ulrich AM, Rwabwogo-Atenyi J, et al. A double-blind comparative clinical trial of mefloquine and chloroquine in symptomatic falciparum malaria. Bull World Health Organ 1983; 61: 713-8
107. ter Kuile FO, Dolan G, Nosten F, et al. Halofantrine versus mefloquine in treatment of multidrug-resistant falciparum malaria. Lancet 1993; 341: 1044-9
108. Looareesuwan S, Wilairatana P, Chokejindachai W, et al. A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 1999; 60: 238-43
109. van Vugt M, Brockman A, Gemperli B, et al. Randomized comparison of artemether-benflumetol and artesunate- mefloquine in treatment of multidrug-resistant falciparum malaria. Antimicrob Agents Chemother 1998; 42: 135-9
110. ter Kuile FO, Nosten F, Luxemburger C, et al. Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. Bull World Health Organ 1995; 73: 631-42
111. ter Kuile FO, Luxemburger C, Nosten F, et al. Predictors of mefloquine treatment failure: a prospective study of 1590 patients with uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg 1995; 89: 660-4
112. Luxemburger C, Price RN, Nosten F, et al. Mefloquine in infants and young children. Ann Trop Paediatr 1996; 16: 281-6
113. Price R, Simpson JA, Teja-Isavatharm P, et al. Pharmacokinetics of mefloquine combined with artesunate in children with acute falciparum malaria. Antimicrob Agents Chemother 1999; 43: 341-6
114. Luxemburger C, van Vugt M, Slight T, et al. Early vomiting of mefloquine in children with malaria is not modified by the timing of antipyretic treatment. Trans R Soc Trop Med Hyg 1998; 92: 562-3
115. Slutsker LM, Khoromana CO, Payne D, et al. Mefloquine therapy for *Plasmodium falciparum* malaria in children under 5 years of age in Malawi: *in vivo/in vitro* efficacy and correlation of drug concentration with parasitological outcome. Bull World Health Organ 1990; 68: 53-9
116. Palmer KJ, Holliday SM, Brogden RN. Mefloquine: a review of its antimalarial activity, pharmacokinetic properties, and therapeutic efficacy. Drugs 1993; 45: 430-75
117. Nosten F, van Vugt. Neuropsychiatric adverse effects of mefloquine: what do we know and what should we do? CNS Drugs 1999; 11 (1): 1-8
118. Phillips-Howard PA, ter Kuile F. CNS adverse events associated with antimalarial agents: fact or fiction? Drug Saf 1995; 12 (6): 370-83
119. Schlagenhauf P. Mefloquine for malaria chemoprophylaxis 1992-1998: a review. J Travel Med 1999; 6: 122-33
120. WHO. Review of central nervous system adverse events related to the antimalarial drug, mefloquine (1985-1990). WHO/MAL/91.1063

121. Weinke T, Trautmann M, Held T, et al. Neuropsychiatric side effects after the use of mefloquine. Am J Trop Med Hyg 1991; 45: 86-91
122. Sowunmi A, Salako LA, Oduola AMJ, et al. Neuropsychiatric side effects of mefloquine in Africans. Trans R Soc Trop Med Hyg 1993; 87: 462-3
123. Luxemburger C, Nosten F, ter Kuile F, et al. Mefloquine for multidrug-resistant malaria [letter]. Lancet 1991; 338: 1268
124. ter Kuile F. Mefloquine, halofantrine and artesunate in the treatment of uncomplicated falciparum malaria in a multidrug resistant area [PhD thesis]. University of Amsterdam, 1994
125. Nguyen TH, Day NP, Ly VC, et al. Post-malaria neurological syndrome. Lancet 1996; 348: 917-21
126. Riemsdijk van RM, van der Klauw MM, van HJ, et al. Neuropsychiatric effects of antimalarials. Eur J Clin Pharmacol 1997; 52: 1-6
127. Sanchez JL, DeFraites RF, Sharp TW, et al. Mefloquine or doxycycline prophylaxis in US troops in Somalia. Lancet 1993; 341: 1021-2
128. Jaspers CA, Hopperus Buma AP, van Thiel PP, et al. Tolerance of mefloquine chemoprophylaxis in Dutch military personnel. Am J Trop Med Hyg 1996; 55: 230-4
129. Hopperus Buma AP, van Thiel PP, Lobel HO, et al. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. J Infect Dis 1996; 173: 1506-9
130. Steffen R, Heusser R, Machler R, et al. Malaria chemoprophylaxis among European tourists in tropical Africa: use adverse reactions, and efficacy. Bull World Health Organ 1990; 68: 313-22
131. Bunnag D, Malikul S, Chittamas S, et al. Fansimef for prophylaxis of malaria: a double-blind randomized placebo controlled trial. Southeast Asian J Trop Med Public Health 1992; 23: 777-82
132. Salako LA, Adio RA, Walker O, et al. Mefloquine-sulphadoxine-pyrimethamine (Fansimef, Roche) in the prophylaxis of *Plasmodium falciparum* malaria: a double-blind, comparative, placebo-controlled study. Ann Trop Med Parasitol 1992; 86: 575-81
133. Boudreau E, Schuster B, Sanchez J, et al. Tolerability of prophylactic Lariam regimens. Trop Med Parasitol 1993; 44: 257-65
134. Bem JL, Kerr L, Stuerchler D. Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions. J Trop Med Hyg 1992; 95: 167-79
135. Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. BMJ 1997; 315: 1412-6
136. Schlagenhauf P, Lobel H, Steffen R, et al. Tolerance of mefloquine by SwissAir trainee pilots. Am J Trop Med Hyg 1997; 56: 235-40
137. Vuurman E, Muntjewerrff N, Uiterwijk M, et al. Effects of mefloquine, alone and with alcohol on psychomotor and driving performance. Eur J Clin Pharmacol 1996; 50: 475-82
138. Hessen-Soderman AC, Bergenius Johan, Palme IB, et al. Mefloquine prophylaxis and hearing, postural control and vestibular functions. J Travel Med 1995; 2: 66-9
139. Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. Clin Exp Dermatol 1999; 24: 263-5
140. Harinasuta T, Bunnag D, Wernsdorfer WH. A phase II clinical trial of mefloquine inpatients with chloroquine-resistant falciparum malaria in Thailand. 1983; 61: 299-305
141. Fonteyne W, Bauwens A, Jordaens L. Atrial flutter with 1:1 conductino after administration of the antimalarial drug mefloquine. Clin Cardiol 1996; 19: 967-8
142. Richter J, Burbach G, Hellgren U, et al. Aberrant atrioventricular conduction triggered by antimalarial prophylaxis with mefloquine. Lancet 1997; 349: 101-2
143. Danis M, Nozais JP, Paris L, et al. Blackwater fever after ingestion of mefloquine: three cases [letter]. Presse Med 1993; 22: 80
144. Van den Ende J, Coppens G, Verstraeten T, et al. Recurrence of blackwater fever: triggering of relapses by different antimalarials. Trop Med Int Health 1998; 3: 632-9
145. Hennequin C, Eouree P, Halfon P. Agranulocytosis during treatment with mefloquine. Lancet 1991; 265: 398-9
146. Gotsman I, Azaz-Livshits T, Fridlender Z, et al. Mefloquine-induced acute hepatitis. Pharmacotherapy 2000; 20: 1517-9
147. Nicolas X, Granier H, Laborde JP, et al. Danger of malaria self-treatment: acute neurologic toxicity of mefloquine and its combination with pyrimethamine-sulfadoxine. Presse Med 2001; 30: 1349-50
148. Steketee RW, Wirima JJ, Slutsker L, et al. Malaria parasite infection during pregnancy and at delivery in mother, placenta, and newborn: efficacy of chloroquine and mefloquine in rural Malawi. Am J Trop Med Hyg 1996; 55 (1 Suppl.): 24-32
149. Nosten F, ter Kuile F, Maelankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. J Infect Dis 1994 169: 595-603
150. McGready R, Cho T, Hkirijaroen L, et al. Quinine and mefloquine in the treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy. Ann Trop Med Parasitol 1998; 92: 643-53
151. Nosten F, Vincenti M, Simpson J, et al. The effects of mefloquine treatment in pregnancy. Clin Infect Dis 1999; 28: 808-15
152. Vanhauwere B, Maradit H, Kerr L. Post-market surveillance of prophylactic mefloquine (Larium®) use in pregnancy. Am J Trop Med Hyg 1998; 58: 17-21
153. Smoak BL, Writer JV, Keep LW, et al. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis 1997; 176: 831-3
154. Edstein MD, Veenendaal JR, Hyslop R. Excretion of mefloquine in human breast milk. Chemotherapy 1988; 34: 165-9
155. International Standard Prescribing Information. Roche, May 1999
156. White NJ, Looareesuwan S, Warrell DA, et al. Quinine loading dose in cerebral malaria. Am J Trop Med Hyg 1983; 31: 1-5
157. Roche RJ, Silamut K, Pukrittayakamee S, et al. Quinine induces reversible high-tone hearing loss. Br J Clin Pharmacol 1990; 29: 780-2
158. Claessen FA, van Boxtel CJ, Perenboom RM, et al. Quinine pharmacokinetics: ototoxic and cardiotoxic effects in healthy Caucasian subjects and in patients with falciparum malaria. Trop Med Int Health 1998; 3: 482-9
159. Waddell K. Blindness from quinine as an antimalarial. Trans R Soc Trop Med Hyg 1996; 90: 331-2
160. Rheeder P, Sieling WL. Acute, persistent quinine-induced blindness: a case report. S Afr Med J 1991; 79: 563-4
161. Yospaiboon Y, Lawtiantong T, Chotibutr S. Clinical observations of ocular quinine intoxication. Jpn J Ophthalmol 1984; 28: 409-15
162. White NJ, Warrell DA, Chanthavanich P, et al. Severe hypoglycaemia and hyperinsulinaemia in falciparum malaria. N Engl J Med 1983; 309: 61-6
163. Okitolonda W, Dellacotte C, Malengreau M, et al. High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. BMJ 1987; 295: 716-8
164. Looareesuwan S, Phillips RE, White NJ, et al. Quinine and severe falciparum malaria in late pregnancy. Lancet 1985; II: 4-8
165. WHO. Severe falciparum malaria: World Health Organization, Communicable Diseases Cluster. Trans R Soc Trop Med Hyg 2000; 94 Suppl. 1: S1-90

166. Taylor WRJ, Prosser DI. Acute rhabdomyolysis, acute renal failure and falciparum malaria [short report]. Trans R Soc Trop Med Hyg 1992; 86: 361
167. Limburg PJ, Katz H, Grant CS, et al. Quinine-induced hypoglycaemia. Ann Intern Med 1993; 119: 218-9
168. White NJ, Looareesuwan S, Warrell DA. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. J Cardiovasc Pharmacol 1983; 5: 173-5
169. Tran TH, Day NP, Nguyen HP, et al. A controlled trial of artemether or quinine in Vietnamese adults with severe falciparum malaria. N Engl J Med 1996; 335: 76-83
170. Na-Bangchang K, Tan-Ariya P, Thanavibul A, et al. Pharmacokinetic and pharmacodynamic interactions of mefloquine and quinine. Int J Clin Pharmacol Res 1999; 19: 73-82
171. Supanaranond W, Suputtamongkol Y, Davis TM, et al. Lack of a significant adverse cardiovascular effect of combined quinine and mefloquine therapy for uncomplicated malaria. Trans R Soc Trop Med Hyg 1997; 91: 694-6
172. Bonington A, Davidson RN, Winstanley PA, et al. Fatal quinine cardiotoxicity in the treatment of falciparum malaria. Trans R Soc Trop Med Hyg 1996; 90: 305-7
173. The Artemether-Quinine Meta-Analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. Trans R Soc Trop Med Hyg 2001; 95: 637-50
174. Bottiger LE, Furhoff AK, Holmberg L. Drug-induced blood dyscrasias: a ten-year material from the Swedish Adverse Drug Reaction Committee. Acta Med Scand 1979; 205: 457-61
175. Danielson DA, Douglas III SW, Herzog P, et al. Drug-induced blood disorders. JAMA 1984; 252: 3257-60
176. Freiman JP. Fatal quinine-induced thrombocytopenia. Ann Intern Med 1990; 112: 308-9
177. Murray JA, Abbott I, Anderson DA, et al. Bitter lemon purpura. BMJ 1979; 2: 1551-2
178. Brasic JR. Quinine-induced thrombocytopenia in a 64-year-old man who consumed tonic water to relieve nocturnal leg cramps. Mayo Clin Proc 2001; 76: 863-4
179. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. BMJ 1995; 310: 13-7
180. Tran TH, Day NP, Ly VC, et al. Blackwater fever in southern Vietnam: a prospective descriptive study of 50 cases. Clin Infect Dis 1996; 23: 1274-81
181. Delacollette C, Taelman H, Wery M. An etiologic study of hemoglobinuria and blackwater fever in the Kivu Mountains, Zaire. Ann Soc Belg Med Trop 1995; 75: 51-63
182. Gottschall JL, Neahring B, McFarland JG, et al. Quinine-induced immune thrombocytopenia with hemolytic uremic syndrome: clinical and serological findings in nine patients and review of literature. Am J Hematol 1994; 47: 283-9
183. Webb RF, Ramirez AM, Hocken AG, et al. Acute intravascular haemolysis due to quinine. N Z Med J 1980; 91: 14-6
184. Spearing RL, Hickton CM, Sizeland P, et al. Quinine-induced disseminated intravascular coagulation. Lancet 1990; 336: 1535-7
185. Maguire RB, Stroncek DF, Campbell AC. Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. Ann Intern Med 1993; 119: 215-7
186. Barr E, Douglas JF, Hill CM. Recurrent acute hypersensitivity to quinine [short report]. BMJ 1990; 301: 323
187. Ljunggren B, Sjovall P. Systemic quinine photosensitivity. Arch Dermatol 1986; 122: 909-11
188. Guzzo C, Kaidbey K. Persistent light reactivity from systemic quinine. Photodermatol Photoimmunol Photomed 1990; 7: 166-8
189. Price EJ, Bevan JS, Rees A. Quinine-induced cutaneous vasculitis. Br J Clin Pract 1992; 46: 138-9
190. Meyrick Thomas RH, Munro DD. Lichen planus in a photosensitive distribution due to quinine. Clin Exp Dermatol 1986; 11: 97-101
191. Dawson TA. Side effect of quinine for nocturnal cramps [letter]. BMJ 1995; 310: 738
192. Hou M, Horney E, Stockelberg D, et al. Multiple quinine-dependent antibodies in a patient with episodic thrombocytopenia, neutropenia, lymphocytopenia, and granulomatous hepatitis. Blood 1997; 90: 4806-11
193. Punukollu RC, Kumar S, Mullen KD. Quinine hepatotoxicity: an underrecognized or rare phenomenon? Arch Intern Med 1990; 150: 1112-3
194. Schapira A, Solomon T, Julien M, et al. Comparison of intramuscular and intravenous quinine for the treatment of severe and complicated malaria in children. Trans R Soc Trop Med Hyg 1993; 87: 299-302
195. Pasvol G, Newton CR, Winstanley PA, et al. Quinine treatment of severe falciparum malaria in African children: a randomized comparison of three regimens. Am J Trop Med Hyg 1991; 45: 702-13
196. Ross R. Intramuscular injections of quinine. J Trop Med Hyg 1914; 17: 286-8
197. Yen LM, Dao LM, Day NP, et al. Role of quinine in the high mortality of intramuscular injection tetanus. Lancet 1994; 344: 786-7
198. Silamut K, Molunto P, Ho M, et al. Alpha 1-acid glycoprotein (orosomucoid) and plasma protein binding of quinine in falciparum malaria. Br J Clin Pharmacol 1991; 32: 311-5
199. Powell RD, McNamara J. Quinine: side-effects and plasma levels. Proceedings of the Helminthological Society of Washington 1966; 30: 331-8
200. Karbwang J, Tin T, Rimchala W, et al. Comparison of artemether and quinine in the treatment of severe falciparum malaria in south-east Thailand. Trans R Soc Trop Med Hyg 1995; 89: 668-71
201. Pukrittayakamee S, Supanaranond W, Looareesuwan S, et al. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. Trans R Soc Trop Med Hyg 1994; 88: 324-7
202. Murphy S, English M, Waruiru C, et al. An open randomized trial of artemether versus quinine in the treatment of cerebral malaria in African children. Trans R Soc Trop Med Hyg 1996; 90: 298-301
203. Bethell DB, Phuong PT, Phuong CX, et al. Electrocardiographic monitoring in severe falciparum malaria. Trans R Soc Trop Med Hyg 1996; 90: 266-9
204. Winstanley PA, Mberu EK, Watkins WM, et al. Towards optimal regimens of parenteral quinine for young African children with cerebral malaria: unbound quinine concentrations following a simple loading dose regimen. Trans R Soc Trop Med Hyg 1994; 88: 577-80
205. White NJ. Optimal regimens of parenteral quinine [letter]. Trans R Soc Trop Med Hyg 1995; 89: 462-4
206. van Hensbroek MB, Kwiatkowski D, van den Berg B, et al. Quinine pharmacokinetics in young children with severe malaria. Am J Trop Med Hyg 1996; 54: 237-42
207. Boland ME, Roper SM, Henry JA. Complications of quinine poisoning. Lancet 1985; I: 384-5
208. Dyson EH, Proudfoot AT, Prescott LF, et al. Death and blindness due to overdose of quinine. BMJ 1985; 291: 31-3
209. Bateman DN, Blain PG, Woodhouse KW, et al. Pharmacokinetics and clinical toxicity of quinine overdosage: lack of efficacy of techniques intended to enhance elimination. Q J Med 1985; 54: 125-31

210. Caminade S, Ricome JL, Auzepy P. Intoxication aigues par quinine, quinidine et chloroquine: a propos de 18 cas. Journal des Agreges 1978; II: 613-8
211. Brinton GS, Norton EW, Zahn JR, et al. Ocular quinine toxicity. Am J Ophthalmol 1980; 90: 403-10
212. Mackie MA, Davidson J, Clarke J. Quinine: acute self-poisoning and ocular toxicity. Scott Med J 1997; 42: 8-9
213. Bacon P, Spalton DJ, Smith SE. Blindness from quinine toxicity. Br J Ophthalmol 1988; 72: 219-24
214. Wolff RS, Wirtschafter D, Adkinson C. Ocular quinine toxicity treated with hyperbaric oxygen. Undersea Hyperb Med 1997; 24: 131-4
215. Dannenberg AL, Dorfman SF, Johnson J. Use of quinine for self-induced abortion. South Med J 1983; 76: 846-9
216. Winckel CWF. Quinine and congenital injuries of ear and eye of the fetus. J Trop Med Hyg 1948; 51: 2-7
217. McGready R, Nosten F. The Thai-Burmese border: drug studies of *Plasmodium falciparum* in pregnancy. Ann Trop Med Parasitol 1999; 93 Suppl. 1: S19-23
218. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. Trans R Soc Trop Med Hyg 2002; 96: 180-4
219. Phillips RE, Looareesuwan S, White NJ, et al. Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. Br J Clin Pharmacol 1986; 21: 677-83
220. Watt G, Na-Nakorn A, Bateman DN, et al. Amplification of quinine cardiac effects by the resistance-reversing agent prochlorperazine in falciparum malaria. Am J Trop Med Hyg 1993; 49: 645-9
221. Baird JK, Basri H, Subianto B, et al. Treatment of chloroquine-resistant Plasmodium vivax with chloroquine and primaquine or halofantrine. J Infect Dis 1995; 17: 1678-82
222. Fryauff DJ, Baird JK, Basri H, et al. Halofantrine and primaquine for radical cure of malaria in Irian Jaya, Indonesia. Ann Trop Med Parasitol 1997; 91: 7-16
223. Brasseur P, Bitsindou P, Moyou RS, et al. Fast emergence of *plasmodium falciparum* resistance to halofantrine. Lancet 1993; 341: 901-2
224. Bouchaud O, Basco LK, Gillotin C, et al. Clinical efficacy and pharmacokinetics of micronized halofantrine for the treatment of acute uncomplicated falciparum malaria in nonimmune patients. Am J Trop Med Hyg 1994; 51: 204-13
225. Karbwang J, Na Bangchang K. Clinical pharmacokinetics of halofantrine. Clin Pharmacokinet 1994; 27: 104-19
226. Vincent MP, Becquart JP, Receveur MC, et al. Halofantrine overdosage [letter]. Presse Med 1992; 21: 131
227. Gillespie SH, Msaki EP, Ramsay A, et al. A new micronized formulation of halofantrine hydrochloride in the treatment of acute *Plasmodium falciparum* malaria. Trans R Soc Trop Med Hyg 1993; 87: 467-9
228. Salako LA, Sowunmi A, Walker O. Evaluation of the clinical efficacy and safety of halofantrine in falciparum malaria in Ibadan, Nigeria. Trans R Soc Trop Med Hyg 1990; 84: 644-7
229. Coulaud JP, Le Bras J, Matheron S, et al. Treatment of imported cases of falciparum malaria in France with halofantrine. Trans R Soc Trop Med Hyg 1986; 80: 615-7
230. Mojon M, Wallon M, Gravey A, et al. Intravascular haemolysis following halofantrine intake [short report]. Trans R Soc Trop Med Hyg 1994; 88: 91
231. Vachon F, Fajac I, Gachot B, et al. Halofantrine and acute intravascular haemolysis. Lancet 1992; 340: 909-10
232. Hasiba K, Os AJ, Schwartz PJ. QT prolongation and ventricular arrhythmias. Ann N Y Acad Sci 1992; 666: 1a-245a
233. Milton KA, Edwards G, Ward SA, et al. Pharmacokinetics of halofantrine in man: effects of food and dose size. Br J Clin Pharmacol 1989; 28: 71-7
234. Monlun E, Le Metayer P, Szwandt S, et al. Cardiac complications of halofantrine: a prospective study of 20 patients. Trans R Soc Trop Med Hyg 1995; 89: 430-3
235. Hombhanje FW, Kereu RK, Bulungol P, et al. Halofantrine in the treatment of uncomplicated falciparum malaria with a three-dose regimen in Papua New Guinea: a preliminary report. P N G Med J 1998; 41: 23-9
236. Touze JE, Bernard J, Keundjian A, et al. Electrocardiographic changes and halofantrine plasma level during acute falciparum malaria. Am J Trop Med Hyg 1996; 54: 225-8
237. Gundersen SG, Rostrup M, von der Lippe E, et al. Halofantrine-associated ventricular fibrillation in a young woman with no predisposing QTc prolongation. Scand J Infect Dis 1997; 29: 207-8
238. Malvy D, Receveur MC, Ozon P, et al. Fatal cardiac incident after use of halofantrine. J Travel Med 2000; 7: 215-6
239. Sowunmi A, Falade CO, Oduola AM, et al. Cardiac effects of halofantrine in children suffering from acute uncomplicated falciparum malaria. Trans R Soc Trop Med Hyg 1998; 92: 446-8
240. Schuster BG, Canfield CJ. Preclinical studies with halofantrine in halofantrine in the treatment of multidrug resistant malaria. Parasitol Today 1989; Suppl.: 65-79
241. Touze JE, Fourcade L, Peyron F, et al. Is halofantrine still advisable in malaria attacks? Ann Trop Med Parasitol 1997; 91: 867-73
242. Matson PA, Luby SP, Redd SC, et al. Cardiac effects of standard-dose halofantrine therapy. Am J Trop Med Hyg 1996; 54: 229-31
243. Berman JD, Nielsen R, Chulay JD, et al. Causal prophylactic efficacy of atovoquone-proguanil (Malarone®) in a human challenge model. Trans R Soc Trop Med Hyg 2001; 95: 429-32
244. Radloff RD, Philipps J, Hutchinson D, et al. Atovoquone plus proguanil is an effective treatment for Plasmodium ovale and P. malariae malaria [short report]. Trans R Soc Trop Med Hyg 1996; 90: 682
245. Looareesuwan S, Wilairatana P, Glanarongran R, et al. Atovaquone and proguanil hydrochloride followed by primaquine for treatment of Plasmodium vivax malaria in Thailand. Trans R Soc Trop Med Hyg 1999; 93: 637-40
246. Lell B, Luckner D, Ndjave M, et al. Randomised placebo-controlled study of atovaquone plus proguanil for malaria prophylaxis in children. Lancet 1998; 351: 709-13
247. Shanks GD, Gordon DM, Klotz FW, et al. Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for *Plasmodium falciparum* malaria. Clin Infect Dis 1998; 27: 494-9
248. Sukwa TY, Mulenga M, Chisdaka NS, et al. A randomised, double-blind, placebo-controlled field trial to determine the efficacy and safety of Malarone (atovaquone/proguanil) for the prophylaxis of malaria in Zambia. Am J Trop Med Hyg 1999; 60: 521-5
249. Hogh B, Clarke PD, Camus D, et al. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet 2000; 356: 1888-94
250. Overbosch D, Schilthuis H, Bienzle U, et al. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travellers: results from a randomized, double-blind study. Clin Infect Dis 2001; 33: 1015-21
251. Bustos DG, Canfield CJ, Canete-Miguel E, et al. Atovaquone-proguanil compared with chloroquine and chloroquine-sulfadoxine-pyrimethamine for treatment of acute *Plasmodium falciparum* malaria in the Philippines. J Infect Dis 1999; 179: 1587-90
252. Rolan PE, Mercer AJ, Weatherley BC, et al. Examination of some factors responsible for a food-induced increase in ab-

sorption of atovaquone. Br J Clin Pharmacol 1994 Jan; 37: 13-20
253. Looareesuwan S, Wilairatana P, Chalermarut K, et al. Efficacy and safety of atovaquone/proguanil compared with mefloquine for treatment of acute *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 1999; 60: 526-32
254. Radloff PD, Philipps J, Nkeyi M, et al. Atovaquone and proguanil for *plasmodium falciparum* malaria. Lancet 1996; 347: 1511-4
255. Bouchaud O, Monlun E, Muanza K, et al. Atovaquone plus proguanil versus halofantrine for the treatment of imported acute uncomplicated *Plasmodium falciparum* malaria in non-immune adults: a randomized comparative trial. Am J Trop Med Hyg 2000; 63: 274-9
256. Looareesuwan S, Chulay JD, Canfield CJ, et al. Malarone (atovaquone and proguanil hydrochloride): a review of its clinical development for treatment of malaria. Malarone Clinical Trials Study Group. Am J Trop Med Hyg 1999; 60: 533-41
257. Ling J, Baird JK, Fryauff DJ, et al. Randomized, placebo-controlled trial of atovaquone/proguanil for the prevention of *Plasmodium falciparum* or Plasmodium vivax malaria among migrants to Papua, Indonesia. Clin Infect Dis 2002; 35: 825-33
258. Malarone® Prescribing Information [online]. Available from URL: www.gsk.com [Accessed 2003 Feb 2]
259. McGready R, Stepniewska K, Edstein MD, et al. The pharmacokinetics of atovaquone and proguanil in pregnant women with acute falciparum malaria. Eur J Clin Pharmacol 2003; 59: 545-52
260. Boots M, Phillips M, Curtis JR. Megaloblastic anemia and pancytopenia due to Proguanil in patients with chronic renal failure. Clin Nephrol 1982; 18: 106-8
261. Basco LK, LeBras J. *In vitro* activity of monodesethylamodiaquine and amopyroquine against African isolates and clones of *Plasmodium falciparum*. Am J Trop Med Hyg 1993; 48: 120-5
262. Long GW, Watt G, Sy N, et al. *In vitro* drug response of *Plasmodium falciparum* in the Philippines: increased resistance to amodiaquine. Southeast Asian J Trop Med Public Health 1987; 18: 202-6
263. Brasseur P, Guiguemede R, Diallo S, et al. Amodiaquine remains effective for treating uncomplicated malaria in west and central Africa. Trans R Soc Trop Med Hyg 1999; 93: 645-50
264. Basco LK. Inefficacy of amodiaquine against chloroquine-resistant malaria [letter]. Lancet 1991; 338: 1460
265. Watt G, Long GW, Padre L, et al. Amodiaquine less effective than chloroquine in the treatment of falciparum malaria in the Philippines. Am J Trop Med Hyg 1987; 36: 3-8
266. White NJ. Can amodiaquine be resurrected? Lancet 1996; 348: 1184-5
267. Adjuik M, Agnamey P, Babiker A, et al. Amodiaquine-artesunate versus amodiaquine for uncomplicated *Plasmodium falciparum* malaria in African children: a randomised, multicentre trial. Lancet 2002; 359: 1365-72
268. Dorsey G, Njama D, Kamya MR, et al. Sulfadoxine/pyrimethamine alone or with amodiaquine or artesunate for treatment of uncomplicated malaria: a longitudinal randomised trial. Lancet 2002; 360: 2031-8
269. Staedke SG, Kamya MR, Dorsey G, et al. Amodiaquine, sulfadoxine/pyrimethamine, and combination therapy for treatment of uncomplicated falciparum malaria in Kampala, Uganda: a randomised trial. Lancet 2001; 358: 368-74
270. Orrell C, Taylor WR, Olliaro P. Acute asymptomatic hepatitis in a healthy normal volunteer exposed to 2 oral doses of amodiaquine and artesunate. Trans R Soc Trop Med Hyg 2001; 95: 517-8
271. Akindele O, Odejide AO. Amodiaquine-induced involuntary movements. BMJ 1976; 2: 214-5
272. Hirst LW, Sanborn G, Green WR, et al. Amodiaquine ocular changes. Arch Opthalmol 1982; 100: 1300-4
273. Hatton CS, Peto TE, Bunch C, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. Lancet 1986; I: 411-4
274. Neftel KA, Woodtly W, Schmid M, et al. Amodiaquine induced agranulocytosis and liver damage. BMJ 1986; 292: 721-3
275. Larrey D, Castot A, Pessayre D, et al. Amodiaquine-induced hepatitis: a report of seven cases. Ann Intern Med 1986; 104: 801-3
276. Bepler CR, Baier HN, McCracken S, et al. A 15 month controlled study of the effects of amodiaquine (Camoquin) in rheumatoid arthritis. Arthritis Rheum 1959; 2: 403-13
277. Clarke JB, Neftel K, Kitteringham NR, et al. Detection of antidrug IgG antibodies in patients with adverse drug reactions to amodiaquine. Int Arch Allergy Appl Immunol 1991; 95: 369-75
278. Christie G, Breckenridge AM, Park BK. Drug-protein conjugates: XVIII. detection of antibodies towards the antimalarial amodiaquine and its quinone imine metabolite in man and the rat. Biochem Pharmacol 1989; 38: 1451-8
279. Luo XD, Shen CC. The chemistry, pharmacology, and clinical applications of qinghaosu (artemisinin) and its derivatives. Med Res Rev 1987; 7: 29-52
280. China Cooperative Research Group on Qinghaosu and its Derivatives as Antimalarials. Clinical studies on the treatment of malaria with Qinghaosu and its derivatives. J Tradit Chin Med 1982; 2: 45-50
281. White NJ. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. Antimicrob Agents Chemother 1997; 41: 1413-22
282. Pukrittayakamee S, Chantra A, Simpson JA, et al. Therapeutic responses to different antimalarial drugs in vivax malaria. Antimicrob Agents Chemother 2000; 44: 1680-5
283. Ribeiro IR, Olliaro P. Safety of artemisinin and its derivatives: a review of published and unpublished clinical trials. Med Trop (Mars) 1998; 58 (3 Suppl.): 50-3
284. Price R, van Vugt M, Phaipun L, et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. Am J Trop Med Hyg 1999; 60: 547-55
285. Leonardi E, Gilvary G, White NJ, et al. Severe allergic reactions to oral artesunate: a report of two cases. Trans R Soc Trop Med Hyg 2001; 95: 182-3
286. Brewer TG, Grate SJ, Peggins JO, et al. Fatal neurotoxicity of arteether and artemether. Am J Trop Med Hyg 1994; 51: 251-9
287. Genovese RF, Newman DB, Petras JM, et al. Behavioral and neural toxicity of arteether in rats. Pharmacol Biochem Behav 1998; 60: 449-58
288. Petras JM, Young GD, Bauman RA, et al. Arteether-induced brain injury in Macaca mulatta: I. the precerebellar nuclei: the lateral reticular nuclei, paramedian reticular nuclei, and perihypoglossal nuclei. Anat Embryol (Berl) 2000; 201: 383-97
289. Nontprasert A, Nosten-Bertrand M, Pukrittayakamee S, et al. Assessment of the neurotoxicity of parenteral artemisinin derivatives in mice. Am J Trop Med Hyg 1998; 59: 519-22
290. Miller L, Panosian CB. Ataxia and slurred speech after artesunate treatment for falciparum malaria [letter]. N Engl J Med 1997; 792: 1328
291. Senanayake N, de Silva HJ. Delayed cerebellar ataxia complicating falciparum malaria: a clinical study of 74 patients. J Neurol 1994; 241: 456-9
292. Van Vugt M, Angus BJ, Price RN, et al. A case-control auditory evaluation of patients treated with artemisinin derivatives for multidrug-resistant *Plasmodium falciparum* malaria. Am J Trop Med Hyg 2000; 62: 65-9
293. Kissinger E, Hien TT, Hung NT, et al. Clinical and neurophysiological study of the effects of multiple doses of artemisinin on

brain-stem function in Vietnamese patients. Am J Trop Med Hyg 2000 Jul-Aug; 63 (1-2): 48-55
294. Dayan AD. Neurotoxicity and artemisinin compounds do the observations in animals justify limitation of clinical use? Med Trop (Mars) 1998; 58 (3 Suppl.): 32-7
295. WHO. The use of artemisinin and its derivatives as anti-malarial drugs: report of a joint CTD/DMP/TDR informal consultation. Geneva: WHO, 1998 Jun 10-12
296. Wang TY. Therapeutic effectiveness and toxic side effects of artemisinin and artemether for their treatment of malaria patients in pregnancy. J Tradit Chin Med 1989; 9: 28-30
297. Li GQ, Guo XB, Yang F. Clinical trials on qinghasou and its derivatives. Vol 1. China: Guangzhou Medicine Institute, 1990
298. McGready R, Cho T, Cho JJ, et al. Artemisinin derivatives in the treatment of falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 1998; 92: 430-3
299. Deen JL, von Seidlein L, Pinder M, et al. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. Trans R Soc Trop Med Hyg 2001; 95: 424-8
300. McGready R, Brockman A, Cho T, et al. Randomized comparison of mefloquine-artesunate versus quinine in the treatment of multidrug-resistant falciparum malaria in pregnancy. Trans R Soc Trop Med Hyg 2000; 94: 689-93
301. McGready R, Cho T, Keo NK, et al. Artemisinin antimalarials in pregnancy: a prospective treatment study of 539 episodes of multidrug-resistant *Plasmodium falciparum*. Clin Infect Dis 2001 Dec 15; 33 (12): 2009-16
302. World Health Organization. Antimalarial drug combination therapy: report of a WHO technical consultation. WHO/CDS/RBM/2001.35
303. von Seidlein L, Milligan P, Pinder M, et al. Efficacy of artesunate plus pyrimethamine-sulphadoxine for uncomplicated malaria in Gambian children: a double-blind, randomised, controlled trial. Lancet 2000; 355: 352-7
304. Doherty JF, Sadiq AD, Bayo L, et al. A randomized safety and tolerability trial of artesunate plus sulfadoxine: pyrimethamine versus sulfadoxine-pyrimethamine alone for the treatment of uncomplicated malaria in Gambian children. Trans R Soc Trop Med Hyg 1999; 93: 543-6
305. Olliaro P, Taylor WR, Rigal J. Controlling malaria: challenges and solutions. Trop Med Int Health 2001; 6: 22-7
306. von Seidlein L, Bojang K, Jones P, et al. A randomized controlled trial of artemether/benflumetol, a new antimalarial and pyrimethamine/sulfadoxine in the treatment of uncomplicated falciparum malaria in African children. Am J Trop Med Hyg 1998; 58: 638-44
307. von Seidlein L, Jaffar S, Pinder M, et al. Treatment of African children with uncomplicated falciparum malaria with a new antimalarial drug, CGP 56697. J Infect Dis 1997; 176: 1113-6
308. Hatz C, Abdulla S, Mull R, et al. Efficacy and safety of CGP 56697 (artemether and benflumetol) compared with chloroquine to treat acute falciparum malaria in Tanzanian children aged 1-5 years. Trop Med Int Health 1998; 3: 498-504
309. Kshirsagar NA, Gogtay NJ, Moorthy NS, et al. A randomized, double-blind, parallel-group, comparative safety, and efficacy trial of oral co-artemether versus oral chloroquine in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in adults in India. Am J Trop Med Hyg 2000; 62: 402-8
310. van Agtmael M, Bouchaud O, Malvy D, et al. The comparative efficacy and tolerability of CGP 56697 (artemether + lumefantrine) versus halofantrine in the treatment of uncomplicated falciparum malaria in travellers returning from the tropics to The Netherlands and France. Int J Antimicrob Agents 1999; 12: 159-69
311. Vugt MV, Wilairatana P, Gemperli B, et al. Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant *Plasmodium falciparum* malaria. Am J Trop Med Hyg 1999; 60: 936-42
312. Bakshi R, Hermeling-Fritz I, Gathmann I, et al. An integrated assessment of the clinical safety of artemether-lumefantrine: a new oral fixed-dose combination antimalarial drug. Trans R Soc Trop Med Hyg 2000; 94: 419-24
313. Bindschedler M, Lefevre G, Ezzet F, et al. Cardiac effects of co-artemether (artemether/lumefantrine) and mefloquine given alone or in combination to healthy volunteers. Eur J Clin Pharmacol 2000; 56: 375-81
314. van Vugt M, Ezzet F, Nosten F, et al. No evidence of cardiotoxicity during antimalarial treatment with artemether-lumefantrine. Am J Trop Med Hyg 1999; 61: 964-7
315. Warhurst DC. Why are primaquine and other 8-aminoquinolines particularly effective against the mature gametocytes and the hypnozoites of malaria [short report]. Ann Trop Med Parasitol 1984; 78: 165
316. Pukrittayakamee S, Vanijanonta S, Chantra A, et al. Blood stage antimalarial efficacy of primaquine in Plasmodium vivax malaria. J Infect Dis 1994; 169: 932-5
317. Arnold J, Alving AS, Hockwald RS. The effect of continuous and intermittent primaquine therapy on the relapse rate of Chesson strain vivax malaria. J Lab Clin Med 1954; 44: 429-38
318. Collins WE, Jeffery GM. Primaquine resistance in Plasmodium vivax. Am J Trop Med Hyg 1996; 55: 243-9
319. Smoak BL, DeFraites RF, Magill AJ, et al. Plasmodium vivax infections in US Army troops: failure of primaquine to prevent relapse in studies from Somalia. Am J Trop Med Hyg 1997; 56: 231-4
320. Doherty JF, Day JH, Warhurst DC, et al. Treatment of Plasmodium vivax malaria: time for a change [short report]. Trans R Soc Trop Med Hyg 1997; 91: 76
321. Bunnag D, Karbwang J, Thanavibul A, et al. High dose of primaquine in primaquine resistant vivax malaria. Trans R Soc Trop Med Hyg 1994; 88: 218-9
322. Clayman CB, Arnold J, Hockwald RS, et al. Toxicity of primaquine in Caucasians. JAMA 1952; 149: 1563-8
323. Clyde DF. Clinical problems associated with the use of primaquine as a tissue schizonticidal and gametocytocidal drug. Bull WHO 1981; 59: 391-5
324. Brennecke FE, Alving AS, Arnold J, et al. A preliminary report on the effect of certain 8-aminoquinolines in the treatment of rheumatoid arthritis. Lab Clin Med 1951; 38: 795-6
325. Hansen JE, Cleve EA, Pruitt FW. Relapse of vivax malaria treated with primaquine and report of one case of cyanosis (methaemoglobinaemia) due to primaquine. Am J Med Sci 1954; 227: 9-12
326. Sietsma Naughton MA, Harley JD. Methaemoglobin levels in soldiers receiving antimalarial drugs. Med J Aust 1971; 27: 473-5
327. Cohen RJ, Sachs JR, Wicker DJ, et al. Methemoglobinemia provoked by malarial chemoprophylaxis in Vietnam. N Engl J Med 1968; 279: 1127-31
328. Fletcher KA, Evans-Price DA, Gilles HM, et al. Studies on the pharmacokinetics of primaquine. Bull WHO 1981; 149: 1563-8
329. Carson PE, Hohl R, Nora MV, et al. Toxicology of the 8-aminoquinolines and genetic factors associated with their toxicity in man. Bull WHO 1981; 59: 427-37
330. Barrett EL. Glucose-6-phosphate dehydrogenase deficiency: a brief review. Trans R Soc Trop Med Hyg 1966; 60: 267-75
331. Zalusky R. Drug-associated hemolytic anemia. Bull N Y Acad Med 1970; 46: 427-37
332. Sarkar S, Prakash D, Marwaha RK, et al. Acute intravascular haemolysis in glucose-6-phosphate deficiency. Ann Trop Paediatr 1993; 13: 391-4
333. Hockwald RS, Arnold J, Clayman C, et al. Toxicity of primaquine in Negroes. JAMA 1952; 149: 1568-70

334. Salvidio E, Pannacciulli I, Tizianello A, et al. Nature of hemolytic crises and the fate of G6PD deficient, drug-damaged erythrocytes in Sardinians. N Engl J Med 1967; 276: 1339-44

335. Khoo KK. The treatment of malaria in glucose-6-phosphate dehydrogenase deficient patients in Sabah. Ann Trop Med Parasitol 1981; 75: 591-5

336. Na Bangchang K, Songsaeng W, Thanavibul A, et al. Pharmacokinetics of primaquine in G6PD deficient and G6PD normal patients with vivax malaria. Trans R Soc Trop Med Hyg 1994; 88: 220-2

337. Abeyaratne KP, Halpe NL. Sensitivity to primaquine in Ceylonese children due to deficiency of erythrocytic glucose-6-phosphate dehydrogenase. Ceylon Med J 1968; 27: 134-8

338. Alving AS, Johnson CF, Tarlov AR, et al. Mitigation of the haemolytic effect of primaquine and enhancement of its action against exoerythrocytic forms of the Chesson strain of Plasmodium vivax by intermittent regimens of drug administration. Bull WHO 1960; 22: 621-31

339. Vivona S, Brewer GJ, Conrad M, et al. The concurrent weekly administration of chloroquine and primaquine for the prevention of Korean vivax malaria. Bull WHO 1961; 25: 267-9

340. Charoenlarp P, Areekul S, Harinasuta T, et al. The haemolytic effect of a single dose of 45mg of primaquine in G-6PD deficient Thais. J Med Assoc Thailand 1972; 55: 631-8

341. Fryauff DJ, Baird JK, Basri H, et al. Randomised placebo-controlled trial of primaquine for prophylaxis of falciparum and vivax malaria. Lancet 1995; 346: 1190-3

342. Baird JK, Lacy MD, Basri H, et al. Randomized, parallel placebo-controlled trial of primaquine for malaria prophylaxis in Papua, Indonesia. Clin Infect Dis 2001; 33: 1990-7

343. Baird JK, Fryauff DJ, Basri H, et al. Primaquine for prophylaxis against malaria among nonimmune transmigrants in Irian Jaya, Indonesia. Am J Trop Med Hyg 1995; 52: 479-84

344. Soto J, Toledo J, Rodriquez M, et al. Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 1998; 129: 241-4

345. Soto J, Toledo J, Rodriquez M, et al. Double-blind, randomized, placebo-controlled assessment of chloroquine/primaquine prophylaxis for malaria in nonimmune Colombian soldiers. Clin Infect Dis 1999; 29: 199-201

346. Weiss WR, Oloo AJ, Johnson A, et al. Daily primaquine is effective for prophylaxis against falciparum malaria in Kenya: comparison with mefloquine, doxycycline, and chloroquine plus proguanil. J Infect Dis 1995; 171: 1569-75

347. Sin DD, Shafran SD. Dapsone- and primaquine-induced methemoglobinemia in HIV-infected individuals. J Acquir Immune Defic Syndr Hum Retrovirol 1996; 12: 477-81

348. White NJ. The treatment of malaria. N Engl J Med 1996; 335: 802-6

349. Luzzi GA, Peto TEA. Adverse effects of antimalarials. Drug Saf 1993; 8 (4): 295-311

Correspondence and offprints: Dr *W. Robert J. Taylor*, WHO/TDR, Avenue Appia 20, Geneva 27, CH 1211, Switzerland.
E-mail: taylorw@who.ch