The following doses are recommended by WHO for the treatment of uncomplicated falciparum malaria.

Artesunate, when used with other antimalarials (amodiaquine, mefloquine, or pyrimethamine-sulfadoxine), is given orally to adults and children in a dose of 4 mg/kg daily, as a single dose, for 3 days.

Artemether is given orally with lumefantrine; 6 doses in total are given, the first at diagnosis and repeated after 8, 24, 36, 48, and 60 hours. Each dose is:

- adults and children weighing over 34 kg, artemether 80 mg with lumefantrine 480 mg
- children 5 to 14 kg, artemether 20 mg with lumefantrine 120 mg
- children 15 to 24 kg, artemether 40 mg with lumefantrine 240 mg
- children 25 to 34 kg, artemether 60 mg with lumefantrine 360 mg

For parenteral use in severe malaria, WHO recommends:

- for adults or children, **artesunate** 2.4 mg/kg intravenously or intramuscularly, repeated after 12 and 24 hours and then once daily thereafter
- as an alternative in children, **artemether** 3.2 mg/kg intramuscularly, followed by 1.6 mg/kg daily thereafter. For both drugs the patient should be transferred to oral therapy as soon as possible

A fixed-dose combination product containing artesunate and amodiaquine (ASAQ) has been developed in order to improve patient adherence and avoid monotherapy, thereby decreasing the risk of acquired drug resistance, and is available in some countries.

Other derivatives of artemisinin, such as artemotil and alpha-beta arteether, are under investigation or commercial development (see Administration of Artemisinin Derivatives, below).

◊ Reviews.

1. McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1999 (accessed 17/05/05).
2. McIntosh HM, Olliaro P. Artemisinin derivatives for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2000 (accessed 17/05/05).
3. Olliaro PL, Taylor WR. Developing artemisinin based drug combinations for the treatment of drug resistant falciparum malaria: a review. *J Postgrad Med* 2004; **50:** 40–4.
4. Ashley EA, White NJ. Artemisinin-based combinations. *Curr Opin Infect Dis* 2005; **18:** 531–6.
5. Davis TME, *et al.* Artemisinin-based combination therapies for uncomplicated malaria. *Med J Aust* 2005; **182:** 181–5.
6. Bukirwa H, Critchley J. Sulfadoxine-pyrimethamine plus artesunate versus sulfadoxine-pyrimethamine plus amodiaquine for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 18/07/06).
7. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. *Clin Pharmacokinet* 2008; **47:** 91–102.

Administration of artemisinin derivatives. To overcome the poor solubility of *artemisinin* in water a number of dosage forms and routes have been tried. Also, several more potent derivatives with more suitable pharmaceutical properties have been developed, notably the methyl ether derivative, *artemether*, and the ethyl ether derivative, *artemotil*, which are more lipid soluble; the sodium salt of the hemisuccinate ester, *sodium artesunate*, which is soluble in water but appears to have poor stability in aqueous solutions; and *sodium artelinate*, which is both soluble and stable in water. Other derivatives that have been studied include *arteflene*.

Several preparations of artemisinin derivatives are available either commercially or for studies organised by bodies such as WHO. These include oral formulations of artemether, artesunate, artemisinin itself, and *artenimol*; intramuscular formulations of artemotil, artemether, and artesunate; intravenous formulations of *artelinic acid* and artesunate; and suppositories of artemisinin, artesunate, and artinimol.

Malaria. The overall management of malaria and the place of artemisinin derivatives in current recommendations are discussed on p.594. In an attempt to delay the development of resistance to these compounds, WHO at one time recommended that their use be restricted to the treatment of malaria in areas of documented multidrug resistance and that they should not be used at all for prophylaxis. However, the development of resistance to conventional treatment has now led WHO to recommend the use in such circumstances of combination therapies containing artemisinin derivatives (artemisinin-based combination therapies, also known as ACTs). The following combination therapies are recommended:

- artemether-lumefantrine
- artesunate plus amodiaquine
- artesunate plus pyrimethamine-sulfadoxine (*Fansidar*)
- artesunate plus mefloquine

Artemether-lumefantrine is now also recommended in the UK as an alternative to quinine-based therapy for uncomplicated falciparum malaria.

In acute uncomplicated malaria artemisinin derivatives are usually given by mouth. Those used have been artemisinin, artemether, or artesunate. Parenteral therapy is generally necessary in severe malaria and WHO recommends[1] artesunate intravenously or intramuscularly in adults and children, or artemether intramuscularly in children, as alternatives to quinine for severe malaria. A systematic review[2] has suggested that intravenous artesunate should be the drug of choice in adults with severe malaria, particularly if acquired in Asia. Rectal artesunate has been successful and is recommended by WHO[1] if parenteral therapy is not possible.

1. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 21/06/06)
2. Jones KL, *et al.* Artesunate versus quinine for treating severe malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 05/06/08).

Schistosomiasis. Findings of a reduced intensity of *Schistosoma mansoni* infection in patients treated with sodium artesunate for malaria[1] prompted further investigation into the use of artemisinin derivatives for the control of schistosomiasis (p.138). A double-blind placebo-controlled study[2] in children negative for *S. mansoni* found a significantly lower incidence of infection in those given artemether orally. There was also a significant reduction in the prevalence of *Plasmodium falciparum* infection. A number of studies in China have confirmed the benefits of artemether or artesunate, often with praziquantel, against *S. japonicum*.[3]

1. De Clercq D, *et al.* Efficacy of artesunate against Schistosoma mansoni infections in Richard Toll, Senegal. *Trans R Soc Trop Med Hyg* 2000; **94:** 90–1.
2. Utzinger J, *et al.* Oral artemether for prevention of Schistosoma mansoni infection: randomised controlled trial. *Lancet* 2000; **355:** 1320–5.
3. Xiao S-H. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. *Acta Trop* 2005; **96:** 153–67.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Arinate; Artesiane; ***Braz.:*** Paluther; Plasmotrim; ***China:*** Cotecxin; ***India:*** Betamotil; E Mal; Falcigo; Falcinil; Larinate; Larither; Mosether; Rapither-AB; ***Neth.:*** Artecef; ***Thai.:*** Plasmotrim†.

Multi-ingredient: ***Austral.:*** Riamet; ***Austria:*** Riamet; ***Belg.:*** Amonate; Co-Arinate; Co-Artesiane; ***China:*** Artemodi; Duo-Cotecxin; ***Cz.:*** Riamet; ***Fr.:*** Riamet; ***Ger.:*** Riamet; ***Gr.:*** Riamet; ***Hong Kong:*** Riamet†; ***India:*** Artemal†; Larimal†; ***Neth.:*** Riamet; ***Norw.:*** Riamet†; ***Port.:*** Riamet; ***S.Afr.:*** Coartem; ***Swed.:*** Riamet; ***Switz.:*** Riamet; ***Thai.:*** Coartem; ***UK:*** Riamet.

Chloroquine *(BAN, rINN)*

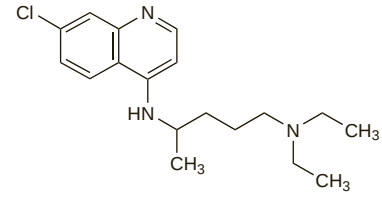
Chloroquinum; Cloroquina; Klorokiini; Klorokin. 4-(7-Chloro-4-quinolylamino)pentyldiethylamine; 7-Chloro-4-(4-diethylamino-1-methylbutylamino)quinoline.

Хлорохин

$C_{18}H_{26}ClN_3$ = 319.9.

CAS — 54-05-7.

ATC — P01BA01.



Pharmacopoeias. In *US*.

USP 31 (Chloroquine). A white or slightly yellow, odourless, crystalline powder. M.p. 87° to 92°. Very slightly soluble in water; soluble in chloroform, in ether, and in dilute acids. Store at a temperature of 25°, excursions permitted between 15° and 30°.

Chloroquine Hydrochloride *(BANM, rINNM)*

Chloroquine, Chlorhydrate de; Chloroquini Hydrochloridum; Hidrocloruro de cloroquina.

Хлорохина Гидрохлорид

$C_{18}H_{26}ClN_3,2HCl$ = 392.8.

CAS — 3545-67-3.

ATC — P01BA01.

Pharmacopoeias. *US* includes an injection.

Chloroquine Phosphate *(BANM, rINNM)*

Chingaminum; Chlorochin-difosfát; Chlorochinium Phosphoricum; Chlorochinum Diphosphoricum; Chlorochiny fosforan; Chlorokvino fosfatas; Chloroquine, phosphate de; Chloroquini Diphosphas; Chloroquini phosphas; Fosfato de cloroquina; Klorokiinifosfaatti; Klorokinfosfat; Klorokin-foszfát; Quingamine; SN-7618.

Хлорохина Фосфат

$C_{18}H_{26}ClN_3,2H_3PO_4$ = 515.9.

CAS — 50-63-5.

ATC — P01BA01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Chloroquine Phosphate). A white or almost white, hygroscopic, crystalline powder. It exists in two forms, one melting at about 195° and the other at about 218°. Freely soluble in water; very slightly soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 3.8 to 4.3. Store in airtight containers. Protect from light.

USP 31 (Chloroquine Phosphate). A white, odourless, crystalline powder, which slowly discolours on exposure to light. It exists in two polymorphic forms, one melting between 193° and 195° and the other between 210° and 215°; mixture of the two forms melts between 193° and 215°. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Its solutions have a pH of about 4.5.

Chloroquine Sulfate *(rINNM)*

Chlorochin-sulfát monohydrát; Chlorochiny siarczan; Chlorokvino sulfatas; Chloroquine, sulfate de; Chloroquine Sulphate *(BANM)*; Chloroquini sulfas; Chloroquini Sulfas Monohydricus; Chloroquini Sulphas; Klorokiinisulfaatti; Klorokinsulfat; Klorokin-szulfát; RP-3377; Sulfato de cloroquina.

Хлорохина Сульфат

$C_{18}H_{26}ClN_3,H_2SO_4,H_2O$ = 436.0.

CAS — 132-73-0 (anhydrous chloroquine sulfate).

ATC — P01BA01.

Pharmacopoeias. In *Eur.* (see p.vii) and *Int.*

Ph. Eur. 6.2 (Chloroquine Sulphate). A white or almost white crystalline powder. Freely soluble in water and in methyl alcohol; very slightly soluble in alcohol. An 8% solution in water has a pH of 4.0 to 5.0. Store in airtight containers. Protect from light.

Sorption. Studies using low concentrations of chloroquine phosphate or chloroquine sulfate indicate that chloroquine exhibits pH-dependent binding to several materials used in medical equipment and membrane filters, including soda glass and various plastics such as cellulose acetate, cellulose propionate, methacrylate butadiene styrene, polypropylene, PVC, ethylvinyl acetate, and polyethylene.[1-3] Although this effect may not be of relevance at doses used clinically,[4] laboratory workers undertaking assays and sensitivity testing must recognise that significant reductions in concentrations can occur when chloroquine is prepared or stored in equipment made from these materials.[2,3] As the effect of borosilicate glass or polystyrene appears to be minimal, it has been suggested that they may be suitable for use in such procedures.[2,3]

Similar sorption has also been reported during membrane filtration of solutions of amodiaquine hydrochloride, mefloquine hydrochloride, or quinine sulfate.[1]

1. Baird JK, Lambros C. Effect of membrane filtration of antimalarial drug solutions on in vitro activity against Plasmodium falciparum. *Bull WHO* 1984; **62:** 439–44.
2. Yahya AM, *et al.* Binding of chloroquine to glass. *Int J Pharmaceutics* 1985; **25:** 217–23.
3. Yahya AM, *et al.* Investigation of chloroquine binding to plastic materials. *Int J Pharmaceutics* 1986; **34:** 137–43.
4. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; **47:** 369–73.

Adverse Effects

Adverse effects experienced with dosage regimens of chloroquine used in the treatment and prophylaxis of malaria are generally less common and less severe than those associated with the higher doses used for prolonged periods in rheumatoid arthritis.

Frequent adverse effects of chloroquine include headache, various skin eruptions, pruritus, and gastrointestinal disturbances such as nausea, vomiting, and diarrhoea. More rarely, mental changes including psychotic episodes, agitation, and personality changes may occur. Convulsions have been reported.

Visual disturbances such as blurred vision and difficulties in focusing have occurred but these are more common with higher doses, when they may be associated with keratopathy or retinopathy, as discussed under Effects on the Eyes, below. Keratopathy usually occurs in the form of corneal opacities and is normally reversible when chloroquine is withdrawn. Retinopathy is the most serious adverse effect of chloroquine on the eyes

and it can result in severe visual impairment. Changes may be irreversible and can even progress after chloroquine is stopped. Those taking high doses of chloroquine for prolonged periods appear to be at greatest risk of developing retinopathy.

Other uncommon adverse effects from prolonged use include loss of hair, bleaching of hair pigment, bluish-black pigmentation of the mucous membranes and skin, photosensitivity, tinnitus, reduced hearing, nerve deafness, neuromyopathy, and myopathy, including cardiomyopathy.

Blood disorders have been reported rarely. They include aplastic anaemia, reversible agranulocytosis, thrombocytopenia, and neutropenia.

There have also been rare reports of changes in liver function, including hepatitis and abnormal liver function tests.

Parenteral therapy with chloroquine can be hazardous and rapid intravenous dosage or the use of high doses can result in cardiovascular toxicity and other symptoms of acute overdosage.

Acute overdosage with chloroquine is extremely dangerous and death can occur within a few hours. Initial effects include headache, gastrointestinal disturbances, drowsiness, and dizziness. Hypokalaemia may occur within a few hours of ingestion of chloroquine. Visual disturbances may be dramatic with a sudden loss of vision. However, the main effect of overdosage with chloroquine is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, coma, and death.

Effects on the blood. Aplastic anaemia was associated with the use of chloroquine in 3 patients.[1] Two patients had received treatment over several months and one of these was later found to have acute myeloblastic leukaemia after receiving chloroquine treatment initially for discoid lupus erythematosus, and later for cerebral malaria. In the third patient aplastic anaemia developed 3 weeks after a short course of chloroquine for malaria.

1. Nagaratnam N, *et al.* Aplasia and leukaemia following chloroquine therapy. *Postgrad Med J* 1978; **54:** 108–12.

Effects on the eyes. The main adverse effects of chloroquine and hydroxychloroquine on the eye are keratopathy and retinopathy.

Keratopathy, characterised by corneal deposits, may occur within a few weeks of starting treatment. However, patients are often asymptomatic and fewer than 50% of affected patients complain of visual symptoms such as photophobia, haloes around lights, or blurred vision. Keratopathy is completely reversible on withdrawal of treatment and is not usually considered to be a contraindication to continued treatment.[1]

Retinopathy is potentially more serious. The outcome on stopping treatment is unpredictable and changes may be irreversible or may even progress.[2,3] Delayed-onset retinopathy has also been reported in patients many years after cessation of treatment.[4] The reported incidence of retinopathy varies according to the methodology and criteria used.[1,5,6] From studies in patients on long-term antimalarial treatment, it was reported[1] that an accumulation of 100 g of chloroquine [phosphate] (250 mg daily for 1 year) might cause retinopathy; the risk was significantly increased as the total dosage exceeded 300 g. Experience in rheumatology also indicates that the incidence of retinal toxicity is dose-related. While the total cumulative dose, the duration of treatment, and the age of the patient might all affect the incidence of retinal toxicity,[7,8] the daily dose might be the most important factor.[9] It has been suggested that the risk of retinal damage is small with daily doses of up to 4.0 mg of chloroquine phosphate per kg body-weight (= chloroquine base approximately 2.5 mg per kg daily) or up to 6.5 mg of hydroxychloroquine sulfate per kg.[9] In obese patients, excessive dosage should be avoided by calculating dosage on the basis of lean body-weight. It appears that retinopathy is rarely, if ever, associated with the weekly dosages of chloroquine recommended for the prophylaxis of malaria.[10,11]

In the UK, a review group[12] convened by the Royal College of Ophthalmologists made **recommendations** regarding use by rheumatologists and dermatologists. Chloroquine should only be used if hydroxychloroquine or other preferred drugs have failed as there is inadequate data to advise on a safe maximum dose; thus the following recommendations relate only to *hydroxychloroquine* as no guidelines have been published for chloroquine.

- Baseline assessment before treatment with hydroxychloroquine is commenced (maximum daily dosage 6.5 mg/kg lean body-weight) should consist of checking renal and hepatic function, questioning the patient about visual impairment not corrected by glasses, and recording near visual acuity.
- Thereafter, patients should be monitored annually with enquiry about visual symptomatology, rechecking of acuity, and assessment for blurred vision.
- Patients should be referred to an ophthalmologist if problems are detected either before or during treatment.
- Those taking long-term hydroxychloroquine should be subject to occasional ophthalmological review after 5 years' continuous treatment.

UK licensed product information for *chloroquine* recommends ophthalmic examination at 3 to 6 monthly intervals in patients receiving continuous high doses for more than a year, or weekly treatment for more than 3 years, or for those in whom total consumption exceeds 100 g or 1.6 g/kg.

1. Bernstein HN. Ophthalmologic considerations and testing in patients receiving long-term antimalarial therapy. *Am J Med* 1983; **75** (suppl 1A): 25–34.
2. Ogawa S, *et al.* Progression of retinopathy long after cessation of chloroquine therapy. *Lancet* 1979; **i:** 1408.
3. Easterbrook M. Ocular effects and safety of antimalarial agents. *Am J Med* 1988; **85** (suppl 4A): 23–9.
4. Ehrenfeld M, *et al.* Delayed-onset chloroquine retinopathy. *Br J Ophthalmol* 1986; **70:** 281–3.
5. Finbloom DS, *et al.* Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol* 1985; **12:** 692–4.
6. Morsman CDG, *et al.* Screening for hydroxychloroquine retinal toxicity: is it necessary? *Eye* 1990; **4:** 572–6.
7. Elman A, *et al.* Chloroquine retinopathy in patients with rheumatoid arthritis. *Scand J Rheumatol* 1976; **5:** 161–6.
8. Marks JS, Power BJ. Is chloroquine obsolete in treatment of rheumatic disease? *Lancet* 1979; **i:** 371–3.
9. Mackenzie AH. Dose refinements in long-term therapy of rheumatoid arthritis with antimalarials. *Am J Med* 1983; **75** (suppl 1A): 40–5.
10. Breckenridge A. Risks and benefits of prophylactic antimalarial drugs. *BMJ* 1989; **299:** 1057–8.
11. Lange WR, *et al.* No evidence for chloroquine-associated retinopathy among missionaries on long-term malaria chemoprophylaxis. *Am J Trop Med Hyg* 1994; **51:** 389–92.
12. Buckley R, *et al.* Royal College of Ophthalmologists, British Association of Dermatologists, and British Society for Rheumatology. Ocular toxicity and hydroxychloroquine: guidelines for screening 2004 (replacing The Royal College of Ophthalmologists Guidelines 1998). Available at: http://www.bad.org.uk/healthcare/guidelines/Ocular_toxicity_and_hydroxychloroquine_guidelines_for_screening_20041.pdf (accessed 09/06/05)

Effects on glucose metabolism. While hypoglycaemia has occurred with quinine (see p.613), it was not generally thought to be associated with chloroquine; however, there has been a report of its occurrence in a patient with reactive hypoglycaemia.[1]

1. Abu-Shakra M, Lee P. Hypoglycemia: an unusual adverse reaction to chloroquine. *Clin Exp Rheumatol* 1994; **12:** 95.

Effects on the heart. Studies in patients with malaria[1] and in healthy subjects[2] indicate that the acute cardiovascular toxicity that may be associated with parenteral use of chloroquine is related to transiently high plasma concentrations produced during the early part of the distribution phase; these findings appear to confirm that the dosage rate is a major determinant of this toxicity. Cardiac conduction abnormalities, including heart block, have also occurred in patients receiving long-term oral therapy with chloroquine,[3] including use in lupus erythematosus,[4,5] as well as after chloroquine overdosage or abuse.[6] Histological changes in endomyocardial biopsy specimens from 2 patients with cardiomyopathy associated with chloroquine or hydroxychloroquine therapy were found to be virtually identical to those seen in the skeletal muscle of patients with chloroquine-induced myopathy[7] (see also Effects on the Muscles, below).

1. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; **155:** 192–201.
2. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; **22:** 31–6.
3. Ogola ESN, *et al.* Chloroquine related complete heart block with blindness: case report. *East Afr Med J* 1992; **69:** 50–2.
4. Piette J-C, *et al.* Chloroquine cardiotoxicity. *N Engl J Med* 1987; **317:** 710–11.
5. Baguet J-P, *et al.* Chloroquine cardiomyopathy with conduction disorders. *Heart* 1999; **81:** 221–3.
6. Ihenacho HNC, Magulike E. Chloroquine abuse and heart block in Africans. *Aust N Z J Med* 1989; **19:** 17–21.
7. Ratliff NB, *et al.* Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. *N Engl J Med* 1987; **316:** 191–3.

Effects on mental function. Serious psychotic effects (depersonalisation and anxiety) developed in a healthy subject who took a standard 3-day course of oral chloroquine for the treatment of *Plasmodium falciparum* malaria, as part of a clinical study. Three weeks after completing the course she still had serious concentration problems and her symptoms gradually resolved over the next 4 months.[1]

1. Telgt DS, *et al.* Serious psychiatric symptoms after chloroquine treatment following experimental malaria infection. *Ann Pharmacother* 2005; **39:** 551–4.

Effects on the muscles. The myopathy induced by chloroquine is characterised by progressive weakness and atrophy of proximal muscles and can develop insidiously after periods of therapy ranging from a few weeks to a few years.[1] There are often mild sensory changes, depression of tendon reflexes, and abnormal nerve conduction studies suggestive of an associated peripheral neuropathy. The myopathy is reversible on withdrawal of treatment but recovery may take several months. Cardiomyopathy may also occur (see under Effects on the Heart, above). Similar effects have been reported with hydroxychloroquine.[2] In a retrospective review of 4405 patients with rheumatic disorders, 214 had received chloroquine or hydroxychloroquine and, of these, 3 developed myopathy.[3]

1. Mastaglia FL. Adverse effects of drugs on muscle. *Drugs* 1982; **24:** 304–21.
2. Estes ML, *et al.* Chloroquine neuromyotoxicity. *Am J Med* 1987; **82:** 447–55.
3. Avina-Zubieta JA, *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.

Effects on the nervous system. Apart from neuropathies (see Effects on the Muscles, above) other adverse effects of chloroquine on the nervous system have included isolated reports of extrapyramidal symptoms and other involuntary movements[1,2] (in patients being treated for malaria), nystagmus[3] (in a patient on prolonged treatment for rheumatoid arthritis), and convulsions[4,5] and nonconvulsive status epilepticus[6] (in patients on malaria prophylaxis).

1. Umez-Eronini EM, Eronini EA. Chloroquine induced involuntary movements. *BMJ* 1977; **1:** 945–6.
2. Singhi S, *et al.* Chloroquine-induced involuntary movements. *BMJ* 1977; **2:** 520.
3. Marks JS. Motor polyneuropathy and nystagmus associated with chloroquine phosphate. *Postgrad Med J* 1979; **55:** 569.
4. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; **297:** 526–7.
5. Fish DR, Espri MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
6. Mülhauser P, *et al.* Chloroquine and nonconvulsive status epilepticus. *Ann Intern Med* 1995; **123:** 76–7.

Effects on the skin. *Pruritus* is common in patients given chloroquine for the treatment of malaria and it may become so severe as to compromise treatment. Itching starts a few hours after use but usually remits spontaneously within 72 hours. Although antihistamines are generally thought ineffective,[1,2] a few patients may obtain some relief.[3] The incidence of pruritus is purported to be higher in black patients, but this may only reflect the greater number of black patients surveyed. The aetiology of this reaction is unknown, but this apparent higher incidence has prompted suggestions that it may have a genetic basis[4] or be related to the affinity of chloroquine for melanin.[2] Chloroquine's main metabolite, monodesethylchloroquine, has been implicated,[5] although there is also some evidence suggesting that patients with pruritus metabolise chloroquine more slowly.[6] A survey[1] in Nigeria found that, of 1100 patients, 74% had pruritus during antimalarial therapy; 61% of these reacted to chloroquine, 30% reacted to amodiaquine, 2.5% to Fansidar (pyrimethamine-sulfadoxine), and, 6.5% reacted to all three. In another study in Nigeria,[4] the incidence of pruritus was reported to be 14% (8 of 56 patients) for chloroquine, 27% (14 of 52) for amodiaquine, and 13% (7 of 53) for halofantrine; none of 58 patients receiving quinine or 82 patients receiving mefloquine had pruritus. In contrast, in a study in Thailand only 1.9% of 1189 chloroquine-treated patients reported pruritus.[7]

There have been rare reports of more severe cutaneous reactions associated with chloroquine, including *toxic epidermal necrolysis*,[8,9] *erythema multiforme*,[10] and *Stevens-Johnson syndrome*,[11] although the causal role of chloroquine is not always clear as some of these patients also received other antimalarials, sometimes at an inappropriate dosage. In a more recent case of toxic epidermal necrolysis,[12] chloroquine given alone for malaria prophylaxis was the probable cause. A young patient receiving radiotherapy developed a localised bullous eruption and rapid progressive moist desquamation on the third day of treatment with oral chloroquine for malaria.[13] For a discussion including the possible effect of chloroquine on the incidence of erythema multiforme in patients taking pyrimethamine with sulfadoxine, see Adverse Effects with Sulfonamides, under Pyrimethamine, p.610.

1. Ajayi AA, *et al.* Epidemiology of antimalarial-induced pruritus in Africans. *Eur J Clin Pharmacol* 1989; **37:** 539–40.
2. Osifo NG. Chloroquine-induced pruritus among patients with malaria. *Arch Dermatol* 1984; **120:** 80–2.
3. Okor RS. Responsiveness of chloroquine-induced pruritus to antihistamine therapy—clinical survey. *J Clin Pharm Ther* 1990; **15:** 147–50.
4. Sowunmi A, *et al.* Pruritus and antimalarial drugs in Africans. *Lancet* 1989; **ii:** 213.
5. Essien EE, *et al.* Chloroquine disposition in hypersensitive and non-hypersensitive subjects and its significance in chloroquine-induced pruritus. *Eur J Drug Metab Pharmacokinet* 1989; **14:** 71–7.
6. Ademowo OG, *et al.* The disposition of chloroquine and its main metabolite desethylchloroquine in volunteers with and without chloroquine-induced pruritus: evidence for decreased chloroquine metabolism in volunteers with pruritus. *Clin Pharmacol Ther* 2000; **67:** 237–41.
7. Bussaratid V, *et al.* Frequency of pruritus in Plasmodium vivax malaria patients treated with chloroquine in Thailand. *Trop Doct* 2000; **30:** 211–14.
8. Kanwar AJ, Singh OP. Toxic epidermal necrolysis—drug induced. *Indian J Dermatol* 1976; **21:** 73–7.
9. Phillips-Howard PA, Warwick Buckler J. Idiosyncratic reaction resembling toxic epidermal necrolysis caused by chloroquine and Maloprim. *BMJ* 1988; **296:** 1605.
10. Steffen R, Somaini B. Severe cutaneous adverse reactions to sulfadoxine-pyrimethamine in Switzerland. *Lancet* 1986; **i:** 610.

11. Bamber MG, *et al.* Fatal Stevens-Johnson syndrome associated with Fansidar and chloroquine. *J Infect* 1986; **13:** 31–3.
12. Boffa MJ, Chalmers RJG. Toxic epidermal necrolysis due to chloroquine phosphate. *Br J Dermatol* 1994; **131:** 444–5.
13. Rustogi A, *et al.* Unexpected skin reaction induced by radiotherapy after chloroquine use. *Lancet Oncol* 2006; **7:** 608–9.

Overdosage. For adverse effects associated with chloroquine overdosage, see Treatment of Adverse Effects, below.

Treatment of Adverse Effects

Acute overdosage with chloroquine can be rapidly lethal and intensive symptomatic supportive treatment should be started immediately. The first steps should be to maintain adequate respiration and to correct any cardiovascular disturbances. Early use of adrenaline with diazepam (see below) may minimise the cardiotoxicity of chloroquine and control arrhythmias. Activated charcoal may be given orally to adults or children who present within 1 hour of ingesting more than the equivalent of 15 mg/kg of chloroquine base; activated charcoal may be left in the stomach to limit any further absorption. Intravenous sodium bicarbonate should be given to correct metabolic acidosis. Other methods to increase the elimination of chloroquine, such as dialysis, are probably of little use.

◊ Chloroquine overdosage is the most severe and frequent cause of intoxication with antimalarial drugs and chloroquine is often used for suicide attempts. Severe toxic manifestations may occur within 1 to 3 hours and fatal outcomes usually occur within 2 to 3 hours of drug ingestion. The major clinical symptoms are of neurological, respiratory, and cardiovascular toxicity;[1] death is usually due to cardiac arrest related to the direct effect of chloroquine on the myocardium.[2] Chloroquine has a low safety margin: doses of 20 mg/kg are considered toxic and 30 mg/kg may be lethal. The mortality rate in some published studies has ranged from 10 to 30%.[1] If gastric lavage is attempted it should be preceded by correction of severe cardiovascular disturbances and institution of artificial ventilation because insertion of the stomach tube may induce sudden cardiac arrest or convulsions; induction of emesis is contra-indicated because of the risk of lung aspiration. Activated charcoal has been recommended to limit absorption of chloroquine that may be left in the gut.[3] There is no evidence to indicate that attempts to increase chloroquine elimination such as acidification of the urine, haemodialysis, peritoneal dialysis, or exchange transfusion, are effective in overdosage. Elimination in the urine is more dependent on haemodynamic status than on infusion of osmotic solutions or acidification. Any clearance achieved by haemoperfusion or haemodialysis is low in comparison with the normal total body clearance.[1]

It is not clear if correction of hypokalaemia is essential, but giving potassium should be avoided in the initial phases of intoxication when conduction disturbances still exist. The degree of hypokalaemia may be correlated with the severity of chloroquine intoxication and might be useful diagnostically.[4] However, chloroquine-induced hypokalaemia may be due to a transport-dependent mechanism rather than to true potassium depletion and overzealous correction could result in hyperkalaemia.[4]

Since there had been no effective treatment for severe chloroquine poisoning, one group of workers tried using early mechanical ventilation, together with adrenaline and high doses of diazepam, both given intravenously, to counteract cardiotoxicity, with encouraging results.[2] Diazepam had earlier been shown to decrease the cardiotoxicity of chloroquine in *animal* studies and there had been several clinical reports of beneficial responses. It was considered that routine use of adrenaline before the onset of cardiac arrhythmia might be beneficial in the treatment of severe chloroquine poisoning.[2] UK licensed product information for chloroquine suggests giving adrenaline by intravenous infusion in a dose of 250 nanograms/kg per minute initially, with increments of 250 nanograms/kg per minute until adequate systolic blood pressure is restored, and diazepam by intravenous infusion in a dose of 2 mg/kg over 30 minutes as a loading dose, followed by 1 to 2 mg/kg per day for up to 2 to 4 days.

Overdosage with hydroxychloroquine has responded to measures similar to those used in the management of chloroquine overdosage.[5]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
2. Riou B, *et al.* Treatment of severe chloroquine poisoning. *N Engl J Med* 1988; **318:** 1–6.
3. Neuvonen PJ, *et al.* Prevention of chloroquine absorption by activated charcoal. *Hum Exp Toxicol* 1992; **11:** 117–20.
4. Clemessy J-L, *et al.* Hypokalaemia related to acute chloroquine ingestion. *Lancet* 1995; **346:** 877–80.
5. Jordan P, *et al.* Hydroxychloroquine overdose: toxicokinetics and management. *J Toxicol Clin Toxicol* 1999; **37:** 861–4.

Precautions

Excessive doses of chloroquine and hydroxychloroquine are associated with retinal or visual field changes and the precautions to be taken in order to minimise such toxicity are discussed under Effects on the Eyes in Adverse Effects, above. There may be a temporary effect on visual accommodation.

Care is necessary when giving chloroquine to patients with hepatic or renal impairment, or to those with severe gastrointestinal disorders, a history of psoriasis, or neurological disorders, especially a history of epilepsy (see below for advice not to use for malaria prophylaxis). Chloroquine should be used with caution in patients with myasthenia gravis as it may aggravate the condition. Patients with G6PD deficiency should be observed for haemolytic anaemia during chloroquine treatment. Full blood counts should be performed at regular intervals during extended treatment with chloroquine. Although there have been reports of fetal abnormalities associated with the use of chloroquine during pregnancy, the risks of malaria are considered to be greater and there appears to be no justification for withholding chloroquine for the treatment or prophylaxis of malaria.

It is important that if chloroquine is given intravenously it should be by slow infusion (typically around 0.8 to 1.25 mg/kg per hour) otherwise severe cardiotoxicity may develop.

Breast feeding. Chloroquine is distributed into breast milk, but not in an amount adequate to provide chemoprophylaxis against malaria for the infant (see under Pharmacokinetics, below). Furthermore, no adverse effects have been seen in breast-feeding infants whose mothers were receiving chloroquine, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 16/04/04)

Epilepsy. After reports[1,2] of convulsions associated with the use of chloroquine for malaria prophylaxis in 4 previously healthy patients and in 2 patients with a history of seizures, it has been suggested that prospective travellers who have a history of epilepsy should be warned of the risk. Although it was initially considered[3] that this should not restrict the use of chloroquine, UK malaria experts have recommended that it should be avoided for malaria prophylaxis in patients with epilepsy.[4]

1. Fish DR, Espir MLE. Convulsions associated with prophylactic antimalarial drugs: implications for people with epilepsy. *BMJ* 1988; **297:** 526–7.
2. Fish DR, Espir MLE. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
3. Hellgren U, Rombo L. Malaria prophylaxis and epilepsy. *BMJ* 1988; **297:** 1267.
4. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Porphyria. Although chloroquine is probably safe in porphyric patients, some authorities consider its use to be contentious. Pyrimethamine is also probably safe in porphyric patients. Other drugs used for prophylaxis, such as dapsone and sulfadoxine and combinations containing them, are definitely contra-indicated in porphyric patients. Quinine is of proven safety in patients with porphyria and cell-culture tests have suggested that proguanil and mefloquine may also be safe.

Chloroquine has been tried in the treatment of porphyria cutanea tarda, but this may be associated with hepatotoxicity (see under Uses, below).

Pregnancy. There has been concern about the potential teratogenic effects of chloroquine because of a few case reports including defects in hearing and vision.[1] Two of 169 infants, born to women given chloroquine 300 mg weekly throughout pregnancy, had birth defects compared with 4 of 454 control infants whose mothers had not received antimalarials; the difference was not significant. The data suggested that chloroquine in the recommended prophylactic doses is not a strong teratogen and that its proved antimalarial benefits outweigh any possible risk of low-grade teratogenicity. Also it has been reported that chloroquine prophylaxis during pregnancy did not affect the birthweight of neonates, compared with a control group.[2]

1. Wolfe MS, Cordero JF. Safety of chloroquine in chemosuppression of malaria during pregnancy. *BMJ* 1985; **290:** 1466–7.
2. Cot M, *et al.* Effect of chloroquine chemoprophylaxis during pregnancy on birth weight: results of a randomized trial. *Am J Trop Med Hyg* 1992; **46:** 21–7.

Psoriatic arthritis. It is recommended that chloroquine and hydroxychloroquine should not be used in the treatment of psoriatic arthritis as exacerbations of skin lesions can occur. Some patients may go on to develop generalised erythroderma with subsequent exfoliative dermatitis.[1] However, there has been controversy over the reported incidence of this adverse effect.[2,3]

1. Slagel GA, James WD. Plaquenil-induced erythroderma. *J Am Acad Dermatol* 1985; **12:** 857–62.
2. Luzar MJ. Hydroxychloroquine in psoriatic arthropathy: exacerbations of psoriatic skin lesions. *J Rheumatol* 1982; **9:** 462–4.
3. Sayers ME, Mazanec DJ. Use of antimalarial drugs for the treatment of psoriatic arthritis. *Am J Med* 1992; **93:** 474–5.

Renal impairment. Although the elimination of chloroquine is prolonged in renal impairment no dosage adjustment is required in the treatment of malaria. Similarly, dosage reduction is not required for chloroquine prophylaxis except in those with severe renal impairment. Doses tend to be reduced when it is given for longer periods to patients with renal impairment.

Interactions

There is an increased risk of inducing ventricular arrhythmias if chloroquine is used with halofantrine (see p.604) or other arrhythmogenic drugs such as amiodarone and moxifloxacin. There is an increased risk of convulsions when chloroquine is given with mefloquine. The absorption of chloroquine can be reduced by antacids or kaolin and its metabolism may be inhibited by cimetidine.

Agalsidase. For the effect of using chloroquine with *agalsidase alfa* or *beta*, see p.2252.

Antiepileptics. Chloroquine may antagonise the antiepileptic activity of *carbamazepine* and *valproate* by lowering the convulsive threshold.

Antimalarials. Chloroquine should not be used with *halofantrine* since the latter prolongs the QT interval and therefore there is an increased potential to induce arrhythmias (see p.604). Use of chloroquine with *mefloquine* increases the risk of convulsions. Also use of chloroquine with *proguanil* may increase the incidence of proguanil-associated mouth ulceration.[1] The activity of chloroquine may be affected when it is given with other *antimalarials*. *Quinine* and chloroquine when used together may be antagonistic.[2] Mixtures of chloroquine with *quinine*, *mefloquine*, *amodiaquine*, *artemisinin*, or *pyrimethamine-sulfadoxine* were antagonistic *in vitro* against *Plasmodium falciparum*.[3]

1. Drysdale SF, *et al.* Proguanil, chloroquine, and mouth ulcers. *Lancet* 1990; **335:** 164.
2. Hall AP. Quinine and chloroquine antagonism in falciparum malaria. *Trans R Soc Trop Med Hyg* 1973; **67:** 425.
3. Stahel E, *et al.* Antagonism of chloroquine with other antimalarials. *Trans R Soc Trop Med Hyg* 1988; **82:** 221.

Antimicrobials. A woman who had previously tolerated chloroquine alone had acute dystonic reactions when also given *metronidazole*.[1] Chloroquine may also reduce the gastrointestinal absorption of *ampicillin* (see p.204).

1. Achumba JI, *et al.* Chloroquine-induced acute dystonic reactions in the presence of metronidazole. *Drug Intell Clin Pharm* 1988; **22:** 308–10.

Ciclosporin. Chloroquine has been reported to increase plasma concentrations of ciclosporin (see p.1826).

Digoxin. Hydroxychloroquine has been reported to increase plasma concentrations of digoxin (see p.1262).

Gastrointestinal drugs. Patients often wish to take chloroquine with food, antacids, or other gastrointestinal drugs to alleviate gastrointestinal irritation. Dosage with *food* may be beneficial as it appears to improve the absorption of chloroquine.[1,2] However, *antacids* or *kaolin* can reduce the absorption of chloroquine and it is therefore recommended that they should be given at least 4 hours apart.[3,4]

Cimetidine and chloroquine should be used with caution as *cimetidine* can significantly reduce the metabolism and elimination of chloroquine and increase its volume of distribution;[5] *ranitidine*, however, appears to have little effect on the pharmacokinetics of chloroquine.[6]

1. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; **23:** 271–3.
2. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; **79:** 559.
3. McElnay JC, *et al.* In vitro experiments on chloroquine and pyrimethamine absorption in the presence of antacid constituents or kaolin. *J Trop Med Hyg* 1982; **85:** 153–8.
4. McElnay JC, *et al.* The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. *J Trop Med Hyg* 1982; **85:** 159–63.
5. Ette EI, *et al.* Chloroquine elimination in humans: effect of low-dose cimetidine. *J Clin Pharmacol* 1987; **27:** 813–16.
6. Ette EI, *et al.* Effect of ranitidine on chloroquine disposition. *Drug Intell Clin Pharm* 1987; **21:** 732–4.

Levothyroxine. For a report of a possible interaction of chloroquine with levothyroxine, see p.2172.

Praziquantel. For a report of possible reduced bioavailability of praziquantel when given with chloroquine, see p.154.

Vaccines. Although chloroquine has been reported to reduce the antibody response to *human diploid rabies vaccine* (see p.2234), the immune response to other vaccines used in routine immunisation schedules (tetanus, diphtheria, measles, poliomyelitis, ty-

phoid, and BCG) has not been found to be altered by chloroquine prophylaxis.[1,2]

1. Greenwood BM. Chloroquine prophylaxis and antibody response to immunisation. *Lancet* 1984; **ii:** 402–3.
2. Wolfe MS. Precautions with oral live typhoid (Ty 21a) vaccine. *Lancet* 1990; **336:** 631–2.

Pharmacokinetics

Chloroquine is rapidly and almost completely absorbed from the gastrointestinal tract when given orally. Absorption is also rapid after intramuscular or subcutaneous use. It is widely distributed into body tissues and has a large apparent volume of distribution. It accumulates in high concentrations in some tissues, such as the kidneys, liver, lungs, and spleen and is strongly bound in melanin-containing cells such as those in the eyes and the skin. It also crosses the placenta. Chloroquine is eliminated very slowly from the body and it may persist in tissues for months or even years after stopping therapy.

Chloroquine is extensively metabolised in the liver, mainly to monodesethylchloroquine with smaller amounts of bisdesethylchloroquine (didesethylchloroquinine) and other metabolites being formed. Monodesethylchloroquine has been reported to have some activity against *Plasmodium falciparum*. Chloroquine and its metabolites are excreted in the urine, with about half of a dose appearing as unchanged drug and about 10% as the monodesethyl metabolite. Chloroquine and its monodesethyl metabolite are both distributed into breast milk.

◊ General references.

1. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine; clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.
2. Ducharme J, Farinotti R. Clinical pharmacokinetics and metabolism of chloroquine: focus on recent advancements. *Clin Pharmacokinet* 1996; **31:** 257–74.

◊ Chloroquine is rapidly absorbed from the gastrointestinal tract but peak plasma concentrations after oral doses can vary considerably.[1] A mean peak plasma concentration of 76 nanograms/mL has been obtained in healthy adults a mean of 3.6 hours after giving the equivalent of 300 mg of chloroquine base orally as tablets.[2] In children with uncomplicated malaria given the equivalent of 10 mg/kg peak plasma concentrations of 250 nanograms/mL have been reached after 2 hours;[3] a mean peak of 134 nanograms/mL has been obtained after 5 hours in healthy children given a similar dose.[4] Nasogastric use has also produced therapeutic concentrations in children with severe falciparum malaria.[5]

Oral bioavailability is increased if chloroquine is taken with food[6,7] and some beverages[8] and may also be affected by the state of health of the patient; mean values have ranged from about 70% in patients with malaria[9] to 78 or 89% in healthy adults.[2] Although oral bioavailability appears to be unaltered in moderately undernourished adults[10] it has been reported that it may be significantly reduced in children with kwashiorkor.[4]

Preliminary studies with chloroquine suppositories indicated that, although rectal bioavailability is less than half of that of oral chloroquine, sustained therapeutic concentrations may be achieved.[11]

Absorption is also rapid after subcutaneous or intramuscular injection and mean peak plasma concentrations of chloroquine have been obtained within about 30 minutes.[5,9,12]

Chloroquine has a large apparent volume of distribution. A multicompartmental model appears to be necessary to describe the distribution kinetics of chloroquine.[2,13] After intravenous dosage there is a multi-exponential decline in plasma concentrations as chloroquine distributes out of a central compartment that has been estimated to be several orders of magnitude smaller than the total volume of distribution.[5,14] This slow distribution out of the central compartment produces transiently high cardiotoxic concentrations of chloroquine if the overall rate of parenteral delivery is not carefully controlled.

Reported mean values for protein binding have ranged from about 58 to 64%.[15,16] Chloroquine is also bound to platelets and granulocytes so that the plasma concentration is only 10 to 15% of that in whole blood.[17] If these cells are not removed by gentle centrifugation during analysis, erroneously high plasma concentrations will be reported. Furthermore, as chloroquine concentrations determined in serum are higher than those in plasma, probably due to release of chloroquine from platelets during coagulation, it is crucial to state whether analysis has been done on whole blood, serum, or properly separated plasma.

About 50% of a dose of chloroquine is metabolised in the liver, mainly to the *N*-dealkylated metabolite monodesethylchloroquine; smaller amounts of bisdesethylchloroquine, 7-chloro-4-aminoquinoline, and *N*-oxidation products are formed. Some of these metabolites may contribute to the cardiotoxicity associated with chloroquine. In one study, peak plasma concentrations of 7-chloro-4-aminoquinoline were found to be twice those of unchanged chloroquine despite the fact that only relatively small amounts are formed; this appears to be due to its fast rate of formation and long elimination half-life.[18]

A mean of 42 to 47% of a dose has been reported to be excreted in the urine as unchanged chloroquine and 7 to 12% as monodesethylchloroquine.[2] Various estimates of the terminal elimination half-life of chloroquine range from several days to up to 2 months, but its slow release from tissues ensures that small amounts may still be detected after a year.[18,19]

1. Hellgren U, *et al.* On the question of interindividual variations in chloroquine concentrations. *Eur J Clin Pharmacol* 1993; **45:** 383–5.
2. Gustafsson LL, *et al.* Disposition of chloroquine in man after single intravenous and oral doses. *Br J Clin Pharmacol* 1983; **15:** 471–9.
3. Adelusi SA, *et al.* Kinetics of the uptake and elimination of chloroquine in children with malaria. *Br J Clin Pharmacol* 1982; **14:** 483–7.
4. Walker O, *et al.* Single dose disposition of chloroquine in kwashiorkor and normal children—evidence for decreased absorption in kwashiorkor. *Br J Clin Pharmacol* 1987; **23:** 467–72.
5. White NJ, *et al.* Chloroquine treatment of severe malaria in children: pharmacokinetics, toxicity, and new dosage recommendations. *N Engl J Med* 1988; **319:** 1493–1500.
6. Tulpule A, Krishnaswamy K. Effect of food on bioavailability of chloroquine. *Eur J Clin Pharmacol* 1982; **23:** 271–3.
7. Lagrave M, *et al.* The influence of various types of breakfast on chloroquine levels. *Trans R Soc Trop Med Hyg* 1985; **79:** 559.
8. Mahmoud BM, *et al.* Significant reduction in chloroquine bioavailability following coadministration with the Sudanese beverages aradaib, karkadi and lemon. *J Antimicrob Chemother* 1994; **33:** 1005–9.
9. White NJ, *et al.* Parenteral chloroquine for treating falciparum malaria. *J Infect Dis* 1987; **155:** 192–201.
10. Tulpule A, Krishnaswamy K. Chloroquine kinetics in the undernourished. *Eur J Clin Pharmacol* 1983; **24:** 273–6.
11. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
12. Phillips RE, *et al.* Divided dose intramuscular regimen and single dose subcutaneous regimen for chloroquine: plasma concentrations and toxicity in patients with malaria. *BMJ* 1986; **293:** 13–16.
13. Frisk-Holmberg M, *et al.* The single dose kinetics of chloroquine and its major metabolite desethylchloroquine in healthy subjects. *Eur J Clin Pharmacol* 1984; **26:** 521–30.
14. Looareesuwan S, *et al.* Cardiovascular toxicity and distribution kinetics of intravenous chloroquine. *Br J Clin Pharmacol* 1986; **22:** 31–6.
15. Walker O, *et al.* Characterization of chloroquine plasma protein binding in man. *Br J Clin Pharmacol* 1983; **15:** 375–7.
16. Ofori-Adjei D, *et al.* Protein binding of chloroquine enantiomers and desethylchloroquine. *Br J Clin Pharmacol* 1986; **22:** 356–8.
17. Gustafsson LL, *et al.* Pitfalls in the measurement of chloroquine concentrations. *Lancet* 1983; **i:** 126.
18. Ette EI, *et al.* Pharmacokinetics of chloroquine and some of its metabolites in healthy volunteers: a single dose study. *J Clin Pharmacol* 1989; **29:** 457–62.
19. Gustafsson LL, *et al.* Chloroquine excretion following malaria prophylaxis. *Br J Clin Pharmacol* 1987; **24:** 221–4.

Distribution into breast milk. Studies[1,2] have suggested that it is safe for mothers to breast feed when they are receiving chloroquine for treatment of malaria. Although chloroquine and its monodesethyl metabolite are distributed into breast milk, it has been estimated that the amount that would be consumed by an infant is well below the therapeutic range and separate chemoprophylaxis for the infant is required.

There appears to be no data on the excretion of hydroxychloroquine in milk after doses appropriate for the prevention or treatment of malaria, but hydroxychloroquine has been detected in breast milk from 2 mothers receiving doses of 400 mg daily for SLE or rheumatoid arthritis.[3,4] One group of workers estimated that, calculated on a body-weight basis, a 9-month-old infant could receive about 2% of a maternal dose via breast feeding.[3]

1. Ogunbona FA, *et al.* Excretion of chloroquine and desethylchloroquine in human milk. *Br J Clin Pharmacol* 1987; **23:** 473–6.
2. Akintonwa A, *et al.* Placental and milk transfer of chloroquine in humans. *Ther Drug Monit* 1988; **10:** 147–9.
3. Nation RL, *et al.* Excretion of hydroxychloroquine in human milk. *Br J Clin Pharmacol* 1984; **17:** 368–9.
4. Østensen M, *et al.* Hydroxychloroquine in human breast milk. *Eur J Clin Pharmacol* 1985; **28:** 357.

Uses and Administration

Chloroquine is a 4-aminoquinoline antimalarial used in the treatment and prophylaxis of malaria. It has also been used in the treatment of hepatic amoebiasis, lupus erythematosus, light-sensitive skin eruptions, and rheumatoid arthritis.

Chloroquine is used for the prophylaxis and treatment of malaria due to susceptible strains of *Plasmodium ovale, P. vivax,* and *P. malariae*. It has also been used for susceptible strains of *P. falciparum* but in most of the world *P. falciparum* is now resistant to chloroquine, which should *not* therefore be given for treatment. Chloroquine is a rapid-acting blood schizontocide with some gametocytocidal activity against *P. ovale, P. vivax, P. malariae,* and immature gametocytes of *P. falciparum*. Since it has no activity against exoerythrocytic forms, it does not produce a radical cure of vivax or ovale malarias. The mechanism of action of chloroquine against blood schizonts remains unclear, but it may influence haemoglobin digestion by raising intravesicular pH in malaria parasite cells. It also interferes with synthesis of nucleoproteins by the parasite.

Chloroquine may be given as the phosphate, sulfate, or hydrochloride. Doses are normally expressed in terms of chloroquine base, and as a general guide:

- chloroquine base 300 mg is equivalent to about chloroquine phosphate 500 mg or chloroquine sulfate 400 mg
- chloroquine base 40 mg is equivalent to about chloroquine hydrochloride 50 mg

Oral bioavailability is increased when chloroquine is taken with food.

For the **treatment of malaria** caused by *P. vivax, P. ovale, P. malariae,* and the few remaining strains of chloroquine-sensitive *P. falciparum,* the usual total oral dose for adults and children is the equivalent of a total of about 25 mg of chloroquine base per kg bodyweight given over 3 days. This total dose has been given in a variety of ways. One way is to give 10 mg/kg, followed after 6 to 8 hours by 5 mg/kg, then 5 mg/kg daily for the next 2 days; alternatively, 10 mg/kg may be given daily for the first 2 days and 5 mg/kg on the third day. Sometimes the adult doses are not expressed in terms of body-weight but as 600 mg followed after 6 to 8 hours by 300 mg, then 300 mg daily for the next 2 days.

In severe and complicated malaria when the patient is unable to take oral medication, if chloroquine is to be used it can be given by injection. The intravenous route is preferred and a slow rate of infusion is essential, the required dose of 25 mg/kg being given in several infusions over 30 to 32 hours. Should the patient recover sufficiently to be able to take chloroquine orally then the intravenous regimen should be halted and oral therapy started.

For **prophylaxis of malaria** in areas where *P. falciparum* is absent or in one of the few remaining areas where it is still sensitive to chloroquine, a dose equivalent to 300 mg of chloroquine base is given once each week, beginning about one week before exposure and continuing throughout, and for at least 4 weeks after, exposure. For children, a weekly dose of 5 mg/kg has been recommended (but see also under Malaria, below). In areas of chloroquine-resistant malaria, but with a low risk of infection, chloroquine is given with proguanil; where there is a high risk of infection alternative antimalarial regimens are recommended.

In the treatment of **hepatic amoebiasis**, chloroquine is used with an intestinal amoebicide. The usual dose is the equivalent of 600 mg of chloroquine base daily for 2 days then 300 mg daily for 2 or 3 weeks. A dose of 6 mg/kg daily up to a maximum of 300 mg daily has been suggested for children.

When chloroquine is used for *long-term therapy* in conditions such as rheumatoid arthritis or lupus erythematosus, the dosage in obese patients should be calculated on the basis of lean body-weight in order to avoid excessive dosage.

In **rheumatoid arthritis**, response to treatment may not be apparent for up to 6 months, but if there is no improvement by then treatment should be stopped. The usual dose is the equivalent of chloroquine base 150 mg daily (maximum 2.5 mg/kg daily) or up to 3 mg/kg daily in children. For precautions and guidelines concerning use by rheumatologists see under Effects on the Eyes, above.

In discoid and systemic **lupus erythematosus** chloroquine is used in a dose equivalent to 150 mg (maximum 2.5 mg/kg) of base daily; children are given a dose of up to 3 mg/kg daily.

In the management of **light-sensitive skin eruptions**, adults may be given the equivalent of 150 to 300 mg of chloroquine base daily during periods of intense light exposure; children may be given up to 3 mg/kg.

Amoebiasis. For a discussion of the treatment of amoebiasis with mention of chloroquine for hepatic amoebiasis, see p.822.

Inflammatory disorders. Chloroquine and hydroxychloroquine possess anti-inflammatory properties and they have been tried or used with some benefit in a range of inflammatory conditions which often have an immunological basis, although they rarely constitute first-line therapy in these disorders. Such conditions include rheumatoid arthritis and SLE (see under Hydroxychloroquine, p.604), ulcerative colitis,[1] infantile interstitial pneumonitis,[2,3] asthma,[4] giant cell arteritis,[5] and various skin disorders (see below). The mode of action in these conditions is unclear. Results of studies have been conflicting but it does appear that chloroquine and hydroxychloroquine might have some immunosuppressive effects.[6,7]

1. Mayer L, Sachar DB. Efficacy of chloroquine in the treatment of inflammatory bowel disease. *Gastroenterology* 1988; **94:** A293.
2. Springer C, *et al.* Chloroquine treatment in desquamative interstitial pneumonia. *Arch Dis Child* 1987; **62:** 76–7.
3. Kerem E, *et al.* Sequential pulmonary function measurements during treatment of infantile chronic interstitial pneumonitis. *J Pediatr* 1990; **116:** 61–7.
4. Charous BL. Open study of hydroxychloroquine in the treatment of severe symptomatic or corticosteroid-dependent asthma. *Ann Allergy* 1990; **65:** 53–8.
5. Le Guennec P, *et al.* Management of giant cell arteritis: value of synthetic antimalarial agents: a retrospective study of thirty six patients. *Rev Rhum* 1994; **61:** 423–8.
6. Bygbjerg IC, Flachs H. Effect of chloroquine on human lymphocyte proliferation. *Trans R Soc Trop Med Hyg* 1986; **80:** 231–5.
7. Prasad RN, *et al.* Immunopharmacology of chloroquine. *Trans R Soc Trop Med Hyg* 1987; **81:** 168–9.

Malaria. The overall treatment and prophylaxis of malaria and the place of chloroquine in current recommendations are discussed on p.594.

TREATMENT. In the treatment of patients with chloroquine-sensitive falciparum malaria studies have found chloroquine to be at least as effective as quinine in both uncomplicated and severe infections. However, very few areas exist where *Plasmodium falciparum* remains sensitive to chloroquine. There are also reports of resistance to chloroquine in *P. vivax*.[1]

Treatment with chloroquine is usually by mouth, adults and children being given the equivalent of 25 mg of chloroquine base per kg body-weight over 3 days. Any chloroquine lost through vomiting needs to be replaced by additional doses.[2]

Intravenous therapy has been used if the infection is severe or oral dosage is not possible. There should be close monitoring for hypotension and other signs of cardiovascular toxicity. The intramuscular or subcutaneous routes have been used if intravenous dosage is not possible. Patients should be transferred to oral therapy as soon as possible and treatment continued until a total dose equivalent to 25 mg of the base per kg has been given.

If injections cannot be given a chloroquine suspension or syrup appears to be well absorbed when given by nasogastric tube even in comatose patients. Rectal use in young children has also produced beneficial responses.[3,4]

PROPHYLAXIS. The widespread prevalence of strains of *P. falciparum* resistant to chloroquine has considerably diminished the value of chloroquine for malaria chemoprophylaxis and has made recommendations increasingly complex (see p.594). If chloroquine is used for prophylaxis it is usually given with proguanil. For **adults** a dose equivalent to 300 mg of chloroquine base is given by mouth once each week, beginning about one week before exposure and continuing throughout, and for at least 4 weeks after, exposure. Some countries advise the use of 100 mg daily for 6 days a week. For **children**, a weekly dose of chloroquine base 5 mg/kg has been recommended, although UK malaria experts[5] have suggested the following prophylactic doses for children based on fractions of the adult dose of 300 mg weekly:

- under 6.0 kg (0 to 12 weeks of age), one-eighth the adult dose
- 6.0 to 9.9 kg (3 to 11 months), one-quarter the adult dose
- 10.0 to 15.9 kg (1 year to 3 years 11 months), three-eighths the adult dose
- 16.0 to 24.9 kg (4 years to 7 years 11 months), half the adult dose
- 25.0 to 44.9 kg (8 years to 12 years 11 months), three-quarters the adult dose
- over 45 kg (13 years and over), the adult dose

They noted that body-weight was a better guide to dosage than age for children over 6 months.

1. Whitby M. Drug resistant Plasmodium vivax malaria. *J Antimicrob Chemother* 1997; **40:** 749–52.
2. WHO. *WHO model formulary*. Geneva: WHO, 2004.
3. Westman L, *et al.* Rectal administration of chloroquine for treatment of children with malaria. *Trans R Soc Trop Med Hyg* 1994; **88:** 446.
4. Antia-Obong OE, *et al.* Chloroquine phosphate suppositories in the treatment of childhood malaria in Calabar, Nigeria. *Curr Ther Res* 1995; **56:** 928–35.
5. Chiodini P, *et al.* HPA Advisory Committee on Malaria Prevention in UK Travellers. Guidelines for malaria prevention in travellers from the United Kingdom (issued 01/07). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496943523 (accessed 17/06/08)

Porphyria cutanea tarda. Chloroquine and hydroxychloroquine have been used with some benefit in the treatment of porphyria cutanea tarda (p.1448) and low doses (such as chloroquine phosphate 125 mg or hydroxychloroquine sulfate 200 mg given twice weekly) have been considered by some to be useful in patients unsuitable for phlebotomy.[1-4] However, the acute increase in urinary porphyrins and fall in hepatic porphyrin content produced by these drugs have been associated with a variable degree of hepatotoxicity[5,6] and others prefer to use desferrioxamine.[7]

1. Grossman ME, *et al.* Porphyria cutanea tarda. *Am J Med* 1979; **67:** 277–86.
2. Cainelli T, *et al.* Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1983; **108:** 593–600.
3. Ashton RE, *et al.* Low-dose oral chloroquine in the treatment of porphyria cutanea tarda. *Br J Dermatol* 1984; **111:** 609–13.
4. Stölzel U, *et al.* Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda. *Arch Dermatol* 2003; **139:** 309–13.
5. Scholnick PL, *et al.* The molecular basis of the action of chloroquine in porphyria cutanea tarda. *J Invest Dermatol* 1973; **61:** 226–32.
6. Rossmann-Ringdahl I, Olsson R. Porphyria cutanea tarda: effects and risk factors for hepatotoxicity from high-dose chloroquine treatment. *Acta Derm Venereol* 2007; **87:** 401–5.
7. Rocchi E. Treatment of porphyria cutanea tarda. *Br J Dermatol* 1987; **116:** 139–40.

Rheumatoid arthritis. For reference to the use of chloroquine in the treatment of rheumatoid arthritis, see under Hydroxychloroquine, p.604.

Sarcoidosis. Chloroquine and hydroxychloroquine have been tried in the management of sarcoidosis (p.1512) as alternatives or adjuncts to corticosteroid therapy.

References.

1. O'Leary TJ, *et al.* The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med* 1986; **315:** 727–30.
2. Adams JS, *et al.* Effective reduction in the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia with short-course chloroquine therapy. *Ann Intern Med* 1989; **111:** 437–8.
3. DeSimone DP, *et al.* Granulomatous infiltration of the talus and abnormal vitamin D and calcium metabolism in a patient with sarcoidosis: successful treatment with hydroxychloroquine. *Am J Med* 1989; **87:** 694–6.
4. Jones E, Callen JP. Hydroxychloroquine is effective therapy for control of cutaneous sarcoidal granulomas. *J Am Acad Dermatol* 1990; **23:** 487–9.
5. Zic JA, *et al.* Treatment of cutaneous sarcoidosis with chloroquine: review of the literature. *Arch Dermatol* 1991; **127:** 1034–40.
6. Baltzan M, *et al.* Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1999; **160:** 192–7.

Skin disorders. In addition to their use in lupus erythematosus hydroxychloroquine and chloroquine have been tried in a number of other skin disorders including polymorphic light eruptions[1] (see Photosensitivity Disorders, p.1581), lichen planus[2,3] (p.1580), cutaneous symptoms of dermatomyositis (p.1510), erythema nodosum,[4,5] and recurrent erythema multiforme (p.1580). It has also been tried in mild type 2 lepra reactions (erythema nodosum leprosum, see p.176).

1. Murphy GM, *et al.* Hydroxychloroquine in polymorphic light eruption: a controlled trial with drug and visual sensitivity monitoring. *Br J Dermatol* 1987; **116:** 379–86.
2. Mostafa WZ. Lichen planus of the nail: treatment with antimalarials. *J Am Acad Dermatol* 1989; **20:** 289–90.
3. De Argila D, *et al.* Isolated lichen planus of the lip successfully treated with chloroquine phosphate. *Dermatology* 1997; **195:** 284–5.
4. Alloway JA, Franks LK. Hydroxychloroquine in the treatment of chronic erythema nodosum. *Br J Dermatol* 1995; **132:** 661–2.
5. Jarrett P, Goodfield MJD. Hydroxychloroquine and chronic erythema nodosum. *Br J Dermatol* 1996; **134:** 373.

Systemic lupus erythematosus. For reference to the use of chloroquine in cutaneous and systemic lupus erythematosus, see Hydroxychloroquine, p.605.

Preparations

BP 2008: Chloroquine Phosphate Tablets; Chloroquine Sulphate Injection; Chloroquine Sulphate Tablets;
USP 31: Chloroquine Hydrochloride Injection; Chloroquine Phosphate Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Nivaquine; ***Austral.:*** Chlorquin; ***Austria:*** Resochin; ***Belg.:*** Nivaquine; ***Braz.:*** Clopirim†; Diclokin; Quinacris; ***Canad.:*** Aralen†; ***Cz.:*** Delagil; ***Denm.:*** Malarex; ***Fin.:*** Heliopar; ***Fr.:*** Nivaquine; ***Ger.:*** Resochin; Weimerquin; ***Hong Kong:*** Syncoquin; ***Hung.:*** Delagil; ***India:*** Clo-Kit; Emquin; Lariago; Maliago; Melubrin; Nivaquine-P; Resochin; ***Indon.:*** Avloclor; Malarex; Mexaquin; Resochin; Riboquin; ***Irl.:*** Avloclor; ***Israel:*** Avloclor; ***Mex.:*** Aralen; Maclorex; Paluken†; ***Neth.:*** Nivaquine; ***NZ:*** Chlorquin; Nivaquine; ***Philipp.:*** Aralen; Chlorofoz; ***Pol.:*** Arechin; ***Port.:*** Resochina; ***Rus.:*** Delagil (Делагил); ***S.Afr.:*** Daramal; Mirquin; Nivaquine; Plasmoquine; ***Spain:*** Resochin; ***Switz.:*** Chlorochin; Nivaquine; ***Thai.:*** Diroquine; Genocin; Maliaquine; P-Roquine†; ***UK:*** Avloclor; Malarivon; Malaviron; Nivaquine; ***USA:*** Aralen.

Multi-ingredient: ***Arg.:*** Tri-Emcortina†; ***Fr.:*** Savarine; ***S.Afr.:*** Daramal-Paludrine†.

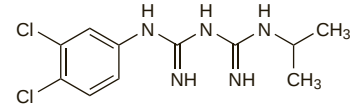
Chlorproguanil Hydrochloride *(BANM, rINNM)*

Chlorproguanil, Chlorhydrate de; Chlorproguanili Hydrochloridum; Hidrocloruro de clorproguanil; M-5943. 1-(3,4-Dichlorophenyl)-5-isopropylbiguanide hydrochloride.

Хлорпрогуанила Гидрохлорид

$C_{11}H_{15}Cl_2N_5,HCl$ = 324.6.

CAS — 537-21-3 (chlorproguanil); 15537-76-5 (chlorproguanil hydrochloride).



(chlorproguanil)

Profile

Chlorproguanil is a biguanide antimalarial used for malaria prophylaxis similarly to proguanil (p.609). It is sometimes given with dapsone. Combination with both dapsone and artesunate is also being investigated for malaria treatment.

◊ Reviews.

1. Bukirwa H, *et al.* Chlorproguanil-dapsone for treating uncomplicated malaria. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 17/05/05).

Halofantrine Hydrochloride *(BANM, USAN, rINNM)*

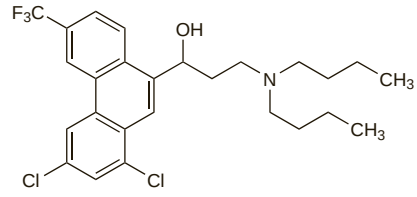
Halofantriinihydrokloridi; Halofantrin hydrochlorid; Halofantrine, Chlorhydrate d'; Halofantrine, chlorhydrate de; Halofantrin-hidroklorid; Halofantrinhydroklorid; Halofantrini hydrochloridum; Halofantrino hidrochloridas; Hidrocloruro de halofantrina; WR-171669. (*RS*)-3-Dibutylamino-1-(1,3-dichloro-6-trifluoromethyl-9-phenanthryl)propan-1-ol hydrochloride; 1,3-Dichloro-α-[2-(dibutylamino)ethyl]-6-trifluoromethyl-9-phenanthrene-methanol hydrochloride.

Галофантрина Гидрохлорид

$C_{26}H_{30}Cl_2F_3NO,HCl$ = 536.9.

CAS — 69756-53-2 (halofantrine); 36167-63-2 (halofantrine hydrochloride); 66051-63-6 (±-halofantrine).

ATC — P01BX01.



(halofantrine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Halofantrine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.

Adverse Effects and Precautions

Adverse effects associated with halofantrine include diarrhoea, abdominal pain, nausea, vomiting, pruritus, and skin rash. Transient elevation of serum transaminases, intravascular haemolysis, and hypersensitivity reactions have also been reported.

Halofantrine can adversely affect the heart particularly by prolonging QT interval. Serious ventricular arrhythmias have been reported and fatalities have occurred. As a result it is contra-indicated in patients known to have a prolonged QT interval or those with cardiac disease or a family history of congenital QT prolongation, and also in those with unexplained syncopal attacks, thiamine deficiency, or electrolyte disturbances, or taking other arrhythmogenic drugs (see also Effects on the Heart, below, and Interactions, below).

Halofantrine is not recommended during pregnancy or breast feeding. It should not be taken on a full stomach since this increases its bioavailability and thus the risk of toxicity; after taking halofantrine, fatty food should be avoided for 24 hours.

Effects on the blood. Halofantrine has been associated with acute intravascular haemolysis.[1,2]

1. Vachon F, *et al.* Halofantrine and acute intravascular haemolysis. *Lancet* 1992; **340:** 909–10.
2. Mojon M, *et al.* Intravascular haemolysis following halofantrine intake. *Trans R Soc Trop Med Hyg* 1994; **88:** 91.

Effects on the heart. Prolonged PR[1,2] and QT[1-5] intervals have been reported in patients given halofantrine and there are individual reports of fatal cardiac arrest[1,5] and of torsade de pointes.[4] In 1994, the UK CSM[6] noted that QT interval prolongation occurred at recommended doses of halofantrine in the ma-