Toxoplasmosis. Pyrimethamine is given, usually with sulfadiazine or another appropriate sulphonamide, in the treatment of toxoplasmosis (p.826). Folinic acid is also given to counteract the megaloblastic anaemia associated with these drugs.

Oral doses suggested by WHO[1] are:

- in *pregnancy* (second and third trimesters), pyrimethamine 25 mg daily for 3 to 4 weeks with sulfadiazine 3 g daily in 4 divided doses
- in *neonates*, pyrimethamine 1 mg/kg daily, with sulfadiazine 85 mg/kg daily in 2 divided doses; treatment should be given for 6 months if there is overt neonatal disease, or for 4 weeks to those without overt disease but whose mother was infected during pregnancy
- in *immunodeficiency*, pyrimethamine 200 mg in divided doses on the first day, then 75 to 100 mg daily for at least 6 weeks, followed by a suppressive dose of 25 to 50 mg daily; sulfadiazine is also given in a dose of 4 to 6 g daily in 4 divided doses for at least 6 weeks, followed by a suppressive dose of 2 to 4 g daily
- in *chorioretinitis*, pyrimethamine 75 mg daily for 3 days, then 25 mg daily for 4 weeks, followed in unresponsive patients by 50 mg daily for a further 4 weeks; sulfadiazine is also given in a dose of 2 g daily in 4 divided doses

Pyrimethamine with clindamycin is an alternative in patients unable to tolerate a sulfonamide.

Other drugs that have been tried with pyrimethamine include azithromycin,[2] clarithromycin,[3] and doxycycline.[4,5]

Alternative regimens tried for long-term maintenance therapy in patients with AIDS have included pyrimethamine plus sulfadiazine given twice weekly[6,7] or pyrimethamine alone in doses of 25 mg or 50 mg daily or 50 mg three times weekly.[8-10] However, results from a study involving 396 patients suggested that the mortality rate was higher in those receiving pyrimethamine 25 mg three times weekly for primary prophylaxis than in those receiving placebo.[11] Pyrimethamine with dapsone given once a week can provide effective prophylaxis but was not well tolerated.[12] Pyrimethamine with sulfadoxine, also given once weekly, was of benefit in bone-marrow transplant recipients.[13]

1. WHO. *WHO model formulary.* Geneva: WHO, 2004.
2. Saba J, *et al.* Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis* 1993; **12:** 853–6.
3. Fernandez-Martin J, *et al.* Pyrimethamine-clarithromycin combination therapy of acute Toxoplasma encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1991; **35:** 2049–52.
4. Morris JT, Kelly JW. Effective treatment of cerebral toxoplasmosis with doxycycline. *Am J Med* 1992; **93:** 107–8.
5. Hagberg L, *et al.* Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis* 1993; **25:** 157–60.
6. Pedrol E, *et al.* Central nervous system toxoplasmosis in AIDS patients: efficacy of an intermittent maintenance therapy. *AIDS* 1990; **4:** 511–17.
7. Podzanczer D, *et al.* Twice-weekly maintenance therapy with sulfadiazine-pyrimethamine to prevent recurrent toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1995; **123:** 175–80.
8. Murphy K, *et al.* Pyrimethamine alone as long-term suppressive therapy in cerebral toxoplasmosis. *Am J Med* 1994; **96:** 95–6.
9. de Gans J, *et al.* Pyrimethamine alone as maintenance therapy for central nervous system toxoplasmosis in 38 patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1992; **5:** 137–42.
10. Leport C, *et al.* Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. *J Infect Dis* 1996; **173:** 91–7.
11. Jacobson MA. *et al.* Primary prophylaxis with pyrimethamine for toxoplasmic encephalitis in patients with advanced human immunodeficiency virus disease: results of a randomized trial. *J Infect Dis* 1994; **169:** 384–94.
12. Opravil M, *et al.* Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1995; **20:** 531–41.
13. Foot ABM, *et al.* Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. *Bone Marrow Transplant* 1994; **14:** 241–5.

Preparations

BP 2008: Pyrimethamine Tablets;
USP 31: Pyrimethamine Tablets; Sulfadoxine and Pyrimethamine Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Daraprim; ***Austral.:*** Daraprim; ***Austria:*** Daraprim; ***Belg.:*** Daraprim; ***Braz.:*** Daraprin; ***Canad.:*** Daraprim; ***Chile:*** Daraprim; ***Fr.:*** Malocide; ***Ger.:*** Daraprim; ***Irl.:*** Daraprim†; ***Israel:*** Daraprim†; ***Malaysia:*** Fansidar; ***Mex.:*** Daraprim; ***Neth.:*** Daraprim; ***Pol.:*** Daraprim; ***S.Afr.:*** Daraprim; ***Spain:*** Daraprim; ***Switz.:*** Daraprim; ***Thai.:*** Daraprim†; ***UK:*** Daraprim; ***USA:*** Daraprim.

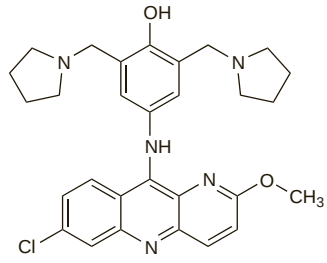
Multi-ingredient: ***Austral.:*** Fansidar; Maloprim; ***Belg.:*** Co-Arinate; Daffafin; Malastop†; ***Braz.:*** Fansidar; ***Canad.:*** Fansidar†; ***Denm.:*** Fansidar†; ***Fr.:*** Fansidar; ***India:*** Artemal†; Laridox; Pyralfin; Pyramet; Rimodar; ***Indon.:*** Fansidar; Suldox; ***Irl.:*** Fansidar; Maloprim†; ***Israel:*** Fansidar; ***Ital.:*** Metakelfin; ***Malaysia:*** Madomine; ***Philipp.:*** Fansidar; ***S.Afr.:*** Fansidar; Maloprim†; ***Singapore:*** Madomine†; Pyrisone; ***Switz.:*** Fansidar; Fansimef†; ***Thai.:*** Vivaxine†; ***UK:*** Fansidar; ***USA:*** Fansidar.

Pyronaridine Phosphate *(rINNM)*

Fosfato de pironaridina; Malaridine Phosphate; Pyronaridine, Phosphate de; Pyronaridini Phosphas. 7-Chloro-2-methoxy-10-[3,5-bis(pyrrolidinomethyl)-4-hydroxyanilino]benzo-[*b*]-1,5-naphthyridine phosphate.

Пиронаридина Фосфат

$C_{29}H_{32}ClN_5O_2,4H_3PO_4$ = 910.0.
CAS — 74847-35-1 (pyronaridine); 76748-86-2 (pyronaridine phosphate).



(pyronaridine)

Pharmacopoeias. In *Chin.*

Profile

Pyronaridine is a naphthyridine derivative used in China in the treatment of vivax malaria and chloroquine-resistant falciparum malaria. Its use has also been investigated in Africa and in Thailand. Combination of pyronaridine with artesunate is also being investigated. Pyronaridine has been given as the phosphate by mouth or by intramuscular or intravenous injection.

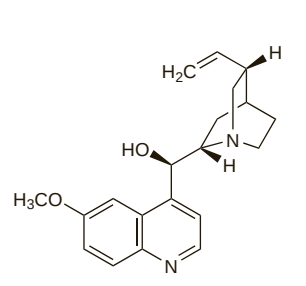
◊ References.

1. Shao B-R. A review of antimalarial drug pyronaridine. *Chin Med J* 1990; **103:** 428–34.
2. Shao B-R, *et al.* A 5-year surveillance of sensitivity in vivo of Plasmodium falciparum to pyronaridine/sulfadoxine/pyrimethamine in Diaoluo area, Hainan province. *Southeast Asian J Trop Med Public Health* 1991; **22:** 65–7.
3. Chen C, *et al.* Studies on a new antimalarial compound: pyronaridine. *Trans R Soc Trop Med Hyg* 1992; **86:** 7–10.
4. Winstanley P. Pyronaridine: a promising drug for Africa? *Lancet* 1996; **347:** 2–3.
5. Ringwald P, *et al.* Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet* 1996; **347:** 24–8.
6. Looareesuwan S, *et al.* Pyronaridine. *Lancet* 1996; **347:** 1189–90.
7. Anonymous. Pyronaridine: yet another promising antimalarial substance from China. *WHO Drug Inf* 1996; **10:** 9–10.
8. Looareesuwan S, *et al.* Clinical study of pyronaridine for the treatment of acute uncomplicated falciparum malaria in Thailand. *Am J Trop Med Hyg* 1996; **54:** 205–9.
9. Ringwald P, *et al.* Efficacy of oral pyronaridine for the treatment of acute uncomplicated falciparum malaria in African children. *Clin Infect Dis* 1998; **26:** 946–53.

Quinine *(BAN)*

Chinina; Chininum; Kiniini; Kinin; Quinina. (8*S*,9*R*)-6′-Methoxycinchonan-9-ol; (α*R*)-α-(6-Methoxy-4-quinolyl)-α-[(2*S*,4*S*,5*R*)-(5-vinylquinuclidin-2-yl)]methanol.

$C_{20}H_{24}N_2O_2$ = 324.4.
CAS — 130-95-0 (anhydrous quinine).
ATC — P01BC01.



Description. Quinine is the chief alkaloid of various species of *Cinchona* (Rubiaceae). It is an optical isomer of quinidine.

Quinine Bisulfate

Chininum Bisulfuricum; Neutral Quinine Sulphate; Quinina, bisulfato de; Quinine Acid Sulphate; Quinine Bisulphate *(BANM)*; Quinini Bisulfas.

$C_{20}H_{24}N_2O_2,H_2SO_4,7H_2O$ = 548.6.
CAS — 549-56-4 (anhydrous quinine bisulfate).
ATC — P01BC01.

Pharmacopoeias. In *Br.*, *Int.*, and *Viet.*

BP 2008 (Quinine Bisulphate). Colourless crystals or a white crystalline powder. It effloresces in dry air. Freely soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 2.8 to 3.4. Protect from light.

Quinine Dihydrochloride *(BANM)*

Chinini Dihydrochloridum; Neutral Quinine Hydrochloride; Quinina, dihidrocloruro de; Quinine Acid Hydrochloride; Quinini Dihydrochloridum.

$C_{20}H_{24}N_2O_2,2HCl$ = 397.3.
CAS — 60-93-5.
ATC — P01BC01.

Pharmacopoeias. In *Br.*, *Chin.*, and *Int.*
Viet. includes the injection.
BP 2008 (Quinine Dihydrochloride). A white or almost white powder. Very soluble in water; soluble in alcohol. A 3% solution in water has a pH of 2.0 to 3.0. Protect from light.

Quinine Etabonate

Euquinina; Euquinine; Quinina, etilcarbonato de; Quinine Ethyl Carbonate.

$C_{23}H_{28}N_2O_4$ = 396.5.
CAS — 83-75-0.
ATC — P01BC01.

Pharmacopoeias. In *Jpn.*

Quinine Hydrobromide *(BANM)*

Basic Quinine Hydrobromide; Chinini Bromidum; Quinina, hidrobromuro de; Quinine Monohydrobromide.

$C_{20}H_{24}N_2O_2,HBr,H_2O$ = 423.3.
CAS — 549-49-5 (anhydrous quinine hydrobromide).
ATC — P01BC01.

Pharmacopoeias. In *Fr.*

Quinine Hydrochloride *(BANM)*

Basic Quinine Hydrochloride; Chinin hydrochlorid dihydrát; Chinini hydrochloridum; Chininii Chloridum; Chininium Chloratum; Chinino hidrochloridas; Chininum Hydrochloricum; Chininy chlorowodorek; Kiniiniihydrokloridi; Kinin-hidroklorid; Kininhydroklorid; Quinina, hidrocloruro de; Quinine, chlorhydrate de; Quinine Monohydrochloride; Quinini Hydrochloridum; Quinini Hydrochloridum Dihydricum.

$C_{20}H_{24}N_2O_2,HCl,2H_2O$ = 396.9.
CAS — 130-89-2 (anhydrous quinine hydrochloride); 6119-47-7 (quinine hydrochloride dihydrate).
ATC — P01BC01.

Pharmacopoeias. In *Eur.* (see p.vii), *Int.*, *Jpn*, and *Viet.*
Ph. Eur. 6.2 (Quinine Hydrochloride). White or almost white, or colourless, fine, silky needles, often grouped in clusters. Soluble in water; freely soluble in alcohol. A 1% solution in water has a pH of 6.0 to 6.8. Protect from light.

Quinine Sulfate

Basic Quinine Sulphate; Chinin sulfát dihydrát; Chinini sulfas; Chinino sulfatas; Chininum Sulfuricum; Chininy siarczan; Kiniinisulfaatti; Kininsulfat; Kinin-szulfát; Quinina, sulfato de; Quinine, sulfate de; Quinine Sulphate *(BANM)*; Quinini Sulfas; Quinini Sulfas Dihydricus.

$(C_{20}H_{24}N_2O_2)_2,H_2SO_4,2H_2O$ = 782.9.
CAS — 804-63-7 (anhydrous quinine sulfate); 6119-70-6 (quinine sulfate dihydrate).
ATC — P01BC01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*
Ph. Eur. 6.2 (Quinine Sulphate). A white or almost white, crystalline powder or fine, colourless needles. Slightly soluble in water; sparingly soluble in boiling water and in alcohol. A 1% suspension in water has a pH of 5.7 to 6.6. Protect from light.
USP 31 (Quinine Sulfate). It is the sulfate of an alkaloid obtained from the bark of species of *Cinchona*. White, odourless, fine needle-like crystals, usually lusterless, making a light and readily compressible mass. It darkens on exposure to light. Soluble 1 in 500 of water and 1 in 120 of alcohol; sparingly soluble in water at 100°; slightly soluble in chloroform; freely soluble in alcohol at 80° and in a mixture of 2 parts of chloroform and one part of dehydrated alcohol; very slightly soluble in ether; Its saturated solution in water is neutral or alkaline to litmus. Protect from light.

Sorption. For reference to loss of quinine sulfate from solutions during membrane filtration, see Chloroquine, p.599.

Adverse Effects

Quinine or its salts given in usual therapeutic doses may give rise to a train of symptoms known as cinchonism, characterised in its mild form by tinnitus, impaired hearing, headache, nausea, and disturbed vision, with, in its more severe manifestations, vomiting, abdominal pain, diarrhoea, and vertigo.

Cinchonism may also occur after small doses in patients hypersensitive to quinine, but urticaria and flushing of the skin with intense pruritus are the most frequent reactions seen in these patients. Other effects include fever, skin rashes, and dyspnoea. Angioedema may also occur and asthma can be precipitated. Thrombocytopenia and other blood disorders have been reported. Thrombocytopenic purpura has been associated with quinine hypersensitivity. Haemoglobinuria occurs rarely.

Other adverse effects of quinine include hypoglycaemia, hypoprothrombinaemia, and renal failure.

The main symptoms of overdosage, which can be fatal, include gastrointestinal effects, oculotoxicity, CNS disturbances, and cardiotoxicity. Visual disturbances including sudden blindness are usually slowly reversible but there may be residual damage. Overdosage is discussed in detail below. Quinine can produce cardiovascular toxicity similar to that seen with quinidine, including conduction disturbances, arrhythmias, anginal symptoms, and hypotension leading to cardiac arrest and circulatory failure. Severe or even fatal cardiovascular toxicity can result from rapid intravenous dosage of quinine.

Large amounts of quinine can induce abortion; congenital malformations, particularly of the optic and auditory nerves, have been reported after failure to induce abortion with quinine. However, quinine should not be withheld from pregnant women with life-threatening malaria (see also under Pregnancy in Precautions, below).

Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; tetanus has developed in some patients (see under Malaria in Uses and Administration, below).

Effects on the blood. Between 1966 and 1975 the Swedish Adverse Drug Reaction Committee received 43 reports of *thrombocytopenia* attributable to quinine or quinidine[1] and the Boston Collaborative Drug Surveillance Program had 11 similar reports in patients studied between 1972 and 1981.[2] The FDA in the USA subsequently received details of 2 fatalities due to quinine-induced thrombocytopenia.[3] Up to October 2004, there had also been 228 cases of thrombocytopenia reported to the Australian Adverse Drug Reactions Advisory Committee, including 6 fatalities.[4] Quinine-induced thrombocytopenia appears to be a hypersensitivity reaction and beverages containing quinine as a bitter in concentrations as low as 20 micrograms/mL have precipitated thrombocytopenic purpura in previously sensitised individuals.[5]

Although quinine can cause *haemolysis*, there is some doubt over the traditional view that irregular dosage with quinine predisposes patients with malaria to *blackwater fever*, a syndrome of severe haemolytic anaemia, haemoglobinuria, oliguria, and renal failure.[6] Some of the patients affected may have had G6PD deficiency.[6] Haemolytic-uraemic syndrome[7-9] and pancytopenia with coagulopathy and renal impairment[10,11] have also been associated with the use of quinine.

There have also been reports of *disseminated intravascular coagulation*, including one fatality, after use of quinine by patients with quinine hypersensitivity.[12-14] In one case[14] the hypersensitivity reaction closely mimicked septic shock.

There have been isolated reports of *agranulocytosis* due to quinine.[15]

1. Böttiger LE, *et al.* Drug-induced blood dyscrasias. *Acta Med Scand* 1979; **205:** 457–61.
2. Danielson DA, *et al.* Drug-induced blood disorders. *JAMA* 1984; **252:** 3257–60.
3. Freiman JP. Fatal quinine-induced thrombocytopenia. *Ann Intern Med* 1990; **112:** 308–9.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; **23:** 20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.htm (accessed 01/11/04)
5. Murray JA, *et al.* Bitter lemon purpura. *BMJ* 1979; **2:** 1551–2.
6. WHO. Severe and complicated malaria. 2nd ed. *Trans R Soc Trop Med Hyg* 1990; **84** (suppl 2): 1–65.
7. Hagley MT, *et al.* Hemolytic-uremic syndrome associated with ingestion of quinine. *Am J Nephrol* 1992; **12:** 192–5.
8. Gottschall JL, *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.
9. McDonald SP, *et al.* Quinine-induced hemolytic uremic syndrome. *Clin Nephrol* 1997; **47:** 397–400.
10. Maguire RB, *et al.* Recurrent pancytopenia, coagulopathy, and renal failure associated with multiple quinine-dependent antibodies. *Ann Intern Med* 1993; **119:** 215–17.
11. Schmitt SK, Tomford JW. Quinine-induced pancytopenia and coagulopathy. *Ann Intern Med* 1994; **120:** 90–1.
12. Spearing RL, *et al.* Quinine-induced disseminated intravascular coagulation. *Lancet* 1990; **336:** 1535–7.
13. Barr E, *et al.* Recurrent acute hypersensitivity to quinine. *BMJ* 1990; **301:** 323.
14. Schattner A. Quinine hypersensitivity simulating sepsis. *Am J Med* 1998; **104:** 488–90.
15. Sutherland R, *et al.* Quinine-induced agranulocytosis: toxic effect of quinine bisulphate on bone marrow cultures in vitro. *BMJ* 1977; **1:** 605–7.

Effects on the ears. Although ototoxicity such as tinnitus or deafness is known to be a possible adverse effect of quinine, reversible hearing loss may also occur. While one group of workers[1] found the reduction in auditory acuity to be greatest at higher frequencies, another group[2] have found that hearing loss was generally equal across the range of frequencies tested and appeared to be related to the plasma concentration of quinine.

1. Roche RJ, *et al.* Quinine induces reversible high-tone hearing loss. *Br J Clin Pharmacol* 1990; **29:** 780–2.
2. Karlsson KK, *et al.* Audiometry as a possible indicator of quinine plasma concentration during treatment of malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 765–7.

Effects on the eyes. Oculotoxicity after overdosage with quinine is well recognised (see below), but there has also been a report of blindness in two patients occurring during supposedly routine therapy.[1]

1. Waddell K. Blindness from quinine as an antimalarial. *Trans R Soc Trop Med Hyg* 1996; **90:** 331–2.

Effects on glucose metabolism. Hypoglycaemia is now recognised to be a frequent complication encountered in falciparum malaria and it is often associated with a poor prognosis. Children, pregnant women, and patients with severe disease appear to be particularly at risk. It is important to recognise that hypoglycaemia rather than cerebral malaria may be the cause of coma. Hypoglycaemia may also be induced by antimalarial therapy; first episodes of hypoglycaemia have been detected after patients received quinine[1-3] or quinidine[4] intravenously, although others have not found that quinine led to the development of hypoglycaemia.[5,6]

Quinine has also been reported to induce hypoglycaemia during treatment for leg cramps.[7]

1. White NJ, *et al.* Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *N Engl J Med* 1983; **309:** 61–6.
2. Okitolonda W, *et al.* High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. *BMJ* 1987; **295:** 716–18.
3. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; **ii:** 4–8.
4. Phillips RE, *et al.* Hypoglycaemia and antimalarial drugs: quinidine and release of insulin. *BMJ* 1986; **292:** 1319–21.
5. Taylor TE, *et al.* Blood glucose levels in Malawian children before and during the administration of intravenous quinine for severe falciparum malaria. *N Engl J Med* 1988; **319:** 1040–7.
6. Kawo NG, *et al.* The metabolic effects of quinine in children with severe and complicated Plasmodium falciparum malaria in Dar es Salaam. *Trans R Soc Trop Med Hyg* 1991; **85:** 711–13.
7. Limburg PJ, *et al.* Quinine-induced hypoglycemia. *Ann Intern Med* 1993; **119:** 218–19.

Effects on the heart. Cardiotoxicity after overdosage with quinine is well recognised, and prolongation of the QT interval has been noted with therapeutic doses. There has also been a report[1] of fatal ventricular fibrillation with QT prolongation in an elderly patient who received standard doses of quinine by slow intravenous infusion for falciparum malaria. It was noted that the patient had some prolongation of the QT interval before starting quinine and also that her free quinine concentrations were unusually high despite total quinine concentrations considered to be within the therapeutic range.

1. Bonington A, *et al.* Fatal quinine cardiotoxicity in the treatment of falciparum malaria. *Trans R Soc Trop Med Hyg* 1996; **90:** 305–7.

Effects on the kidneys. See Effects on the Blood, above.

Effects on the liver. Although hepatitis has been associated with quinidine therapy (see p.1383), there appear to be few reports of hepatotoxicity due to quinine usage. Granulomatous hepatitis has been reported in 2 patients taking quinine,[1,2] but the diagnosis in the first of these cases was challenged as the histological findings were considered to be more indicative of non-specific reactive hepatitis.[3] Hepatotoxicity due to quinine hypersensitivity has been reported in another patient.[4] Symptoms of hepatotoxicity occurred within 24 hours in a further patient taking quinine for nocturnal leg cramps.[5]

1. Katz B, *et al.* Quinine-induced granulomatous hepatitis. *BMJ* 1983; **286:** 264–5.
2. Mathur S, *et al.* Quinine induced granulomatous hepatitis and vasculitis. *BMJ* 1990; **300:** 613.
3. Nirodi NS. Quinine induced granulomatous hepatitis. *BMJ* 1983; **286:** 647.
4. Punukollu RC, *et al.* Quinine hepatotoxicity: an underrecognized or rare phenomenon? *Arch Intern Med* 1990; **150:** 1112–13.
5. Farver DK, Lavin MN. Quinine-induced hepatotoxicity. *Ann Pharmacother* 1999; **33:** 32–4.

Effects on the skin. Urticaria, cutaneous flushing, various skin rashes, and pruritus are the commonest symptoms of hypersensitivity reactions to quinine.

Topical contact with quinine may cause contact as well as photocontact allergy, but quinine can also induce photosensitivity reactions after systemic dosage.[1,2] Photosensitivity associated with quinine intake from excessive consumption of tonic water has been reported.[3] There have also been reports of eczematous dermatitis,[1] oedema and erythema,[4] and lichen planus.[4] Both phototoxic[4] and photoallergic[1] mechanisms have been suggested. Fatal cutaneous vasculitis related to quinine treatment for nocturnal cramps has been reported.[5]

For a comparison of the incidence of pruritus induced by various antimalarials, see under Chloroquine, p.600.

1. Ljunggren B, Sjövall P. Systemic quinine photosensitivity. *Arch Dermatol* 1986; **122:** 909–11.
2. Ljunggren B, *et al.* Systemic quinine photosensitivity with photoepicutaneous cross-reactivity to quinidine. *Contact Dermatitis* 1992; **26:** 1–4.
3. Wagner GH, *et al.* 'I'll have mine with a twist of lemon': quinine photosensitivity from excessive intake of tonic water. *Br J Dermatol* 1994; **131:** 734–5.
4. Ferguson J, *et al.* Quinine induced photosensitivity: clinical and experimental studies. *Br J Dermatol* 1987; **117:** 631–40.
5. Price EJ, *et al.* Quinine-induced cutaneous vasculitis. *Br J Clin Pract* 1992; **46:** 138–9.

Hypersensitivity. For reference to hypersensitivity reactions associated with quinine, see Effects on the Blood, Effects on the Liver, and Effects on the Skin, above.

Overdosage. Cinchonism may occur with therapeutic doses of quinine and symptoms include nausea, vomiting, tinnitus, deafness, headache, vasodilatation, and slightly disturbed vision. These symptoms may also occur in acute overdosage, but the visual disorders may be severe and there may be CNS disturbances and cardiotoxicity. A lethal dose or lethal plasma-quinine concentration has not been established but fatalities have been reported[1] in adults after doses of 2 to 8 g and in children after 1 g.

An analysis[2] of 165 cases of acute quinine poisoning revealed that: 21% had no symptoms, nausea with or without vomiting occurred in 47%, visual disturbances in 42%, tinnitus in 38%, other auditory disturbances in 23%, sinus tachycardia in 23%, and other ECG abnormalities in 8%. Mild impairment of consciousness was reported in 14% of the patients while 7 (4%) patients had deeper grades of coma. Of the 5 patients who died, 4 developed intractable ventricular arrhythmias and the fifth had a Jacksonian fit followed by cardiac arrest.

The effects of oculotoxicity may include blurred vision, defective colour perception, visual field constriction, and total blindness.[2,3] The onset of symptoms may vary from a few hours to a day or more after ingestion.[2,3] Suggested mechanisms for the oculotoxicity of quinine include an action on the retinal vasculature to produce ischaemia or a direct toxic effect on the retina.[1] Visual loss in one group of patients[3] was associated with plasma-quinine concentrations in excess of 10 micrograms/mL. However, in another group plasma-quinine concentrations were considered to be an imprecise guide to predicting visual disturbances.[2] The speed and degree of visual recovery varies. Of 70 patients with visual disturbances after quinine poisoning, 39 subsequently had a period of total blindness.[2] Permanent visual deficits remained in 19 of these but no patient had permanent bilateral blindness. All of the 31 patients who had had blurred vision recovered full visual acuity.

It is considered that the actions of quinine on the myocardium are similar to those of quinidine but that it is less potent.[1] Sinus tachycardia and minor ECG changes are the most common cardiovascular effects. Conduction abnormalities and ventricular dysrhythmias may occur with severe poisoning. Ventricular tachycardia is mostly associated with cardiogenic shock or circulatory collapse. Hypokalaemia may also occur.[1]

1. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
2. Boland ME, *et al.* Complications of quinine poisoning. *Lancet* 1985; **i:** 384–5.
3. Dyson EH, *et al.* Death and blindness due to overdose of quinine. *BMJ* 1985; **291:** 31–3.

Treatment of Adverse Effects

In acute overdosage with quinine or its salts multiple doses of activated charcoal may be given to adults or children who present within one hour of ingesting more than the equivalent of 30 mg/kg of quinine base or any amount in a child under 2 years of age; gastric lavage may also be considered for use in adults. Other measures aimed at enhancing the elimination of quinine are largely ineffective. Treatment is mostly symptomatic with attention being given to maintaining blood pressure, respiration, and renal function, and to treating arrhythmias.

Vasodilators and stellate ganglion block have been used to prevent or reverse visual impairment but there is little evidence to support their use.

◊ It has been suggested that, as quinine has antimuscarinic effects, gastric emptying may be delayed and considerable amounts of drug might be removed from the stomach beyond the usual 4 hours.[1] Others consider that gastric lavage is of doubtful value as quinine is rapidly absorbed and vomiting has often occurred before admission.[2] However, studies in healthy subjects and poisoned patients suggest that oral activated charcoal may increase the elimination of quinine.[3,4] Other methods of increasing elimination are probably ineffective. In a study involving 16 patients with quinine poisoning forced acid diuresis, haemodial-

ysis, haemoperfusion, or plasma exchange were all found to be ineffective in increasing quinine elimination.[5]

Stellate ganglion block has been recommended to prevent or reverse retinal damage, the rationale being that quinine-induced oculotoxicity might arise from retinal arteriolar constriction. However, clinical studies have failed to find sufficient improvement to justify its use.[6,7] Intravenous nitrates produced beneficial responses in 2 patients.[8]

1. Boland M, Volans G. ABC of poisoning: miscellaneous drugs. *BMJ* 1984; **289:** 1361–5.
2. Jaeger A, *et al.* Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2:** 242–73.
3. Lockey D, Bateman DN. Effect of oral activated charcoal on quinine elimination. *Br J Clin Pharmacol* 1989; **27:** 92–4.
4. Prescott LF, *et al.* Treatment of quinine overdosage with repeated oral charcoal. *Br J Clin Pharmacol* 1989; **27:** 95–7.
5. Bateman DN, *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.
6. Boland ME, *et al.* Complications of quinine poisoning. *Lancet* 1985; **i:** 384–5.
7. Dyson EH, *et al.* Quinine amblyopia: is current management appropriate? *J Toxicol Clin Toxicol* 1985–6; **23:** 571–8.
8. Moore D, *et al.* Research into quinine ocular toxicity. *Br J Ophthalmol* 1992; **76:** 703.

Precautions

Quinine and its salts are contra-indicated in patients with a history of hypersensitivity to quinine or quinidine and in patients with tinnitus or optic neuritis. They should not be used in the presence of haemolysis. They should be used with caution in patients with atrial fibrillation, cardiac conduction defects, or heart block. Quinine should be avoided in patients with myasthenia gravis as it may aggravate their condition.

Pregnancy in a patient with malaria is not generally regarded as a contra-indication to the use of quinine.

As quinine has been implicated in precipitating blackwater fever it is generally contra-indicated in patients who have already suffered an attack. Quinine may also cause haemolysis in some types of G6PD deficiency and should be used with care.

It is important that when quinine is given intravenously it should be given by slow infusion and the patient observed closely for signs of cardiotoxicity. Blood-glucose concentrations should also be monitored. Problems that have been associated with intramuscular use are discussed under Malaria in Uses and Administration, below.

Breast feeding. Although quinine is distributed into breast milk in small amounts,[1] the American Academy of Pediatrics considers that the use of quinine is probably compatible with breast feeding.[2]

1. Phillips RE, *et al.* Quinine pharmacokinetics and toxicity in pregnant and lactating women with falciparum malaria. *Br J Clin Pharmacol* 1986; **21:** 677–83.
2. 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 19/04/04)

Liver disease. See under Pharmacokinetics, below.

Porphyria. For a discussion of the problems of the use of antimalarials in patients with porphyria and a comment that quinine is considered to be safe for use in such patients, see under Precautions for Chloroquine, p.601.

Pregnancy. The use of quinine in large doses as an abortifacient in the past has led to concern over its use during pregnancy, but no evidence of an oxytocic effect was found when it was used to treat severe falciparum malaria in women in the third trimester of pregnancy.[1]

Congenital abnormalities including damage to the auditory and optic nerves have been seen, usually after attempted abortions, but WHO[2] considers quinine to be safe when used in normal therapeutic doses during pregnancy (although the problem of hypoglycaemia in the second and third trimesters may mean that artemisinin derivatives are preferred). Jitteriness attributed to quinine withdrawal has been reported in an infant whose mother had drunk large quantities of tonic water containing quinine during the last 17 weeks of pregnancy.[3]

As malaria is potentially serious during pregnancy and poses a threat to the mother and fetus, there appears to be little justification for withholding treatment in the absence of a suitable alternative. However, pregnant patients treated for malaria are at special risk from hypoglycaemia exacerbated or caused by quinine-induced hyperinsulinaemia (see under Effects on Glucose Metabolism in Adverse Effects, above) and should be managed appropriately.

1. Looareesuwan S, *et al.* Quinine and severe falciparum malaria in late pregnancy. *Lancet* 1985; **ii:** 4–8.
2. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 07/07/06)
3. Evans ANW, *et al.* The ingestion by pregnant women of substances toxic to the foetus. *Practitioner* 1980; **224:** 315–19.

Renal impairment. See under Pharmacokinetics, below.

Interactions

As quinine shares many of the actions of quinidine, interactions seen between quinidine and other drugs (see p.1384) might also occur with quinine. Both have actions on skeletal muscle and may potentiate the effects of drugs with neuromuscular-blocking activity (see under Antiarrhythmics on p.1903). There is an increased risk of inducing ventricular arrhythmias if quinine is given with halofantrine (see p.604) or other arrhythmogenic drugs such as amiodarone, the antihistamines astemizole and terfenadine, cisapride, and the antipsychotic pimozide. There may be an increased risk of convulsions when quinine is given with mefloquine.

Amantadine. For a report of quinine reducing renal clearance of amantadine, see Antiarrhythmics, p.793.

Anticoagulants. Quinine can cause hypoprothrombinaemia and thereby enhance the effect of anticoagulants. In one report, reductions in *warfarin* dosage were necessary after ingestion of large amounts of tonic water containing quinine (see p.1429).

Antimalarials. Quinine and *chloroquine* may be antagonistic when used for falciparum malaria (see p.601). For a report of quinine reducing plasma concentrations of *primaquine*, see p.608.

Ciclosporin. For a report of quinine decreasing plasma concentrations of ciclosporin, see p.1826.

Digoxin. Quinidine has been reported to increase serum-digoxin concentrations (see Quinidine under Antiarrhythmics, p.1261) and quinine has reduced total body clearance of digoxin (see Antimalarials, p.1262).

Flecainide. For a report of quinine inhibiting the metabolism of flecainide, see p.1289.

Histamine H_2-antagonists. *Cimetidine* has been reported to reduce the clearance of quinine and prolong its elimination half-life in a study in healthy subjects; no significant effect was seen with *ranitidine*.[1]

1. Wanwimolruk S, *et al.* Effects of cimetidine and ranitidine on the pharmacokinetics of quinine. *Br J Clin Pharmacol* 1986; **22:** 346–50.

Rifampicin. Elimination of quinine has been reported to increase in patients also receiving rifampicin.[1]

1. Wanwimolruk S, *et al.* Marked enhancement by rifampicin and lack of effect of isoniazid on the elimination of quinine in man. *Br J Clin Pharmacol* 1995; **40:** 87–91.

Tobacco smoking. A single-dose study in healthy subjects has suggested that blood concentrations of quinine are lower in heavy smokers than in non-smokers, potentially impairing efficacy.[1]

1. Wanwimolruk S, *et al.* Cigarette smoking enhances the elimination of quinine. *Br J Clin Pharmacol* 1993; **36:** 610–14.

Pharmacokinetics

The pharmacokinetics of quinine are altered significantly by malaria infection, the major effects being reductions in both its apparent volume of distribution and its clearance.

Quinine is rapidly and almost completely absorbed from the gastrointestinal tract and peak concentrations in the circulation are attained about 1 to 3 hours after oral doses of the sulfate or bisulfate. Plasma protein binding is about 70% in healthy subjects and rises to 90% or more in patients with malaria. Quinine is widely distributed throughout the body. Concentrations attained in the CSF of patients with cerebral malaria have been reported to be about 2 to 7% of those in the plasma.

Quinine is extensively metabolised in the liver and rapidly excreted mainly in the urine. Estimates of the proportion of unchanged quinine excreted in the urine vary from less than 5 to 20%. Excretion is increased in acid urine. The elimination half-life is about 11 hours in healthy subjects but may be prolonged in patients with malaria. Small amounts of quinine also appear in the bile and saliva.

Quinine crosses the placenta and is distributed into breast milk (see Breast Feeding, above).

◊ References.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Supanaranond W, *et al.* Disposition of oral quinine in acute falciparum malaria. *Eur J Clin Pharmacol* 1991; **40:** 49–52.
3. Wanwimolruk S, *et al.* Pharmacokinetics of quinine in young and elderly subjects. *Trans R Soc Trop Med Hyg* 1991; **85:** 714–17.
4. Dyer JR, *et al.* The pharmacokinetics and pharmacodynamics of quinine in the diabetic and non-diabetic elderly. *Br J Clin Pharmacol* 1994; **38:** 205–12.
5. Sowunmi A, Salako LA. Effect of dose size on the pharmacokinetics of orally administered quinine. *Eur J Clin Pharmacol* 1996; **49:** 383–6.
6. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine: clinical implications. *Clin Pharmacokinet* 1996; **30:** 263–99.
7. Boele van Hensbroek M, *et al.* Quinine pharmacokinetics in young children with severe malaria. *Am J Trop Med Hyg* 1996; **54:** 237–42.
8. Zhang H, *et al.* Evidence for involvement of human CYP3A in the 3-hydroxylation of quinine. *Br J Clin Pharmacol* 1997; **43:** 245–52.
9. Viriyayudhakorn S, *et al.* Pharmacokinetics of quinine in obesity. *Trans R Soc Trop Med Hyg* 2000; **94:** 425–8.

Administration in liver disease. Reduced clearance of quinine and prolonged elimination half-life have been reported in patients with acute hepatitis B given a single intravenous dose.[1] The results suggested that quinine accumulation after multiple doses could be greater in patients with hepatitis, even once hepatic function had returned to normal. In another study[2] patients with moderate chronic liver disease were given quinine orally; the half-life was prolonged but total clearance was not affected.

1. Karbwang J, *et al.* The pharmacokinetics of quinine in patients with hepatitis. *Br J Clin Pharmacol* 1993; **35:** 444–6.
2. Auprayoon P, *et al.* Pharmacokinetics of quinine in chronic liver disease. *Br J Clin Pharmacol* 1995; **40:** 494–7.

Administration in renal impairment. As urinary clearance comprises only 20% of total clearance of quinine, it appears that high plasma concentrations reported in patients with severe falciparum malaria and acute renal failure may be related more to the severity of the malaria, and associated pharmacokinetic changes, rather than to any reduction in the glomerular filtration rate.[1] There were significant changes in the pharmacokinetics of quinine in 6 patients with chronic renal failure after a single oral dose.[2] The changes included a prolonged half-life, but there was no clear relationship between severity of renal failure and the degree of impairment of quinine clearance.

1. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10:** 187–215.
2. Rimchala P, *et al.* Pharmacokinetics of quinine in patients with chronic renal failure. *Eur J Clin Pharmacol* 1996; **49:** 497–501.

Uses and Administration

Quinine is a cinchona alkaloid and a 4-methanolquinoline antimalarial that is a rapid-acting blood schizontocide with activity against *Plasmodium falciparum, P. vivax, P. ovale,* and *P. malariae*. It is active against the gametocytes of *P. malariae* and *P. vivax*, but not against mature gametocytes of *P. falciparum*. The precise mechanism of action of quinine is unclear but it may interfere with lysosome function or nucleic acid synthesis in the malaria parasite. Since it has no activity against exoerythrocytic forms, quinine does not produce a radical cure in vivax or ovale malarias. The increasing spread of resistance to chloroquine has been responsible for the re-emergence of quinine as an important drug in the treatment of falciparum malaria. Quinine is not generally used for malaria prophylaxis.

Quinine is also used to treat the protozoal infection babesiosis and for the relief of nocturnal leg cramps.

Quinine has mild analgesic and antipyretic properties and is sometimes included in preparations used for the symptomatic relief of the common cold and influenza; additional salts that have been used for this purpose include the camsilate and the gluconate.

Quinine is also used as a bitter and a flavour.

Quinine is given as a number of salts and 100 mg of anhydrous quinine is equivalent to about:

- 169 mg of quinine bisulfate
- 122 mg of quinine dihydrochloride
- 122 mg of quinine etabonate
- 130 mg of quinine hydrobromide
- 122 mg of quinine hydrochloride
- 121 mg of quinine sulfate

For the treatment of **malaria** quinine is given orally, usually as the sulfate, hydrochloride, or dihydrochloride, or parenterally as the dihydrochloride; quinine

etabonate is sometimes used orally because unlike other quinine salts, which are intensely bitter, it is tasteless. They all contain about the same amount of quinine and any of them can be used when the dose is cited in terms of "quinine salt"; this is not the case for the bisulfate, which contains a correspondingly smaller amount of quinine. Quinine formate is sometimes given parenterally.

A course of treatment with quinine for falciparum malaria usually lasts 7 days and in uncomplicated infections treatment should preferably be given by the oral route. The usual *oral* dose is 600 mg of quinine salt given every 8 hours for 7 days. For children, a dose of 10 mg of quinine salt per kg body-weight given every 8 hours for 7 days is recommended.

In severe or complicated falciparum malaria, or when the patient is unable to take oral medication, quinine should be given parenterally by slow intravenous infusion, but this can be hazardous and patients generally need monitoring, particularly for signs of cardiotoxicity. Therapy should be changed to the oral route as soon as possible to complete the course. To obtain therapeutic concentrations rapidly with parenteral therapy, quinine is often given in an initial loading dose followed by maintenance doses. A recommended *intravenous* dosage regimen suggested by WHO is an initial loading dose of 20 mg of quinine dihydrochloride per kg (up to a maximum of 1.4 g) given over 4 hours with maintenance infusions being started 8 hours later, calculated from the start of the previous infusion. Alternatively, in intensive care units, an initial loading dose of 7 mg/kg may be given over 30 minutes followed immediately by the first of the maintenance infusions. Maintenance infusions consist of 10 mg/kg (up to a maximum of 700 mg) given over 4 hours every 8 hours. A loading dose should not be given if the patient has received quinine, quinidine, mefloquine, or halofantrine, during the previous 24 hours. If parenteral therapy is required for more than 48 hours the maintenance dose of quinine dihydrochloride should be reduced to 5 to 7 mg/kg.

If intravenous infusion is not possible, quinine dihydrochloride has been given *intramuscularly*. Doses, including the loading dose, are the same as those used intravenously; the drug should be diluted in sodium chloride 0.9% to a concentration of 60 to 100 mg of the dihydrochloride per mL, and the total dose divided between two injection sites, preferably each anterior thigh (not the buttock). However, intramuscular injection can be irritant and there have been concerns regarding its safety and efficacy (see under Malaria, below).

When used for the relief of nocturnal **leg cramps**, quinine is given at night in an oral dose of 200 to 300 mg of the sulfate or bisulfate. Quinine benzoate has also been used.

Babesiosis. Although there is no established specific treatment for babesiosis (p.823), a combination of quinine and clindamycin has been used for *Babesia microti* infections.[1,2] For suggested doses see under Clindamycin, p.253. Quinine with azithromycin was reported to be effective in a patient who had not responded to quinine with clindamycin.[3]

1. Abramowicz M., ed. *Drugs for parasitic infections*. 1st ed. New Rochelle NY: The Medical Letter. 2007.
2. Wormser GP, *et al.* The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2006; **43:** 1089–1134. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/508667 (accessed 17/06/08)
3. Shaio MF, Yang KD. Response of babesiosis to a combined regimen of quinine and azithromycin. *Trans R Soc Trop Med Hyg* 1997; **91:** 214–15.

Flavouring. The Joint FAO/WHO Expert Committee on Food Additives concluded that quinine levels in soft drinks of up to 100 mg/litre (as quinine base) were not of toxicological concern.[1] However, because of the possibility of hypersensitivity reactions in some individuals, the committee recommended that consumers be informed of the presence of quinine in food or beverages.

1. FAO/WHO. Evaluation of certain food additives and contaminants: forty-first report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 837* 1993.

Malaria. Quinine has had an important role in the treatment of falciparum malaria (see p.594) being used where there is chloroquine or multidrug *Plasmodium falciparum* resistance,[1-4] and also (in view of the widespread problem of *P. falciparum* resistance) where the infective species is not known, or if the infection is mixed. Treatment should be with one of the quinine salts given orally, with a dose of 600 mg of quinine salt for adults, or 10 mg/kg for children, every 8 hours for 7 days. The dose of quinine salt applies to the hydrochloride, dihydrochloride, sulfate, and etabonate, but not to the bisulfate. Any quinine lost through vomiting within one hour of an oral dose should be replaced by additional doses.[1]

The oral route may not provide effective treatment in severe infection and in such cases quinine should be given as the dihydrochloride by slow intravenous infusion, with the patient being observed closely, particularly for any signs of cardiotoxicity.[4] Loading doses of quinine are often used to obtain therapeutic blood concentrations as soon as possible in severely ill patients but they should not be given to patients who have received quinine, quinidine, mefloquine, or halofantrine, within the previous 24 hours.

WHO[3,4] has given recommendations for intravenous regimens comprising an initial loading dose and maintenance infusions (for details see Uses and Administration, above). Patients are transferred to oral therapy as soon as possible, and treatment continued until a total of at least 7 days of therapy has been given. If intravenous formulations of quinine are unavailable quinidine may be used as an alternative; for further details, see under the Uses and Administration of Quinidine, p.1385.

If facilities for intravenous infusion, including monitoring, are not available quinine may be given by deep intramuscular injection.[4] A loading dose of quinine dihydrochloride 20 mg/kg is given by injection in divided sites followed by injections of 10 mg/kg every 8 hours;[4] a dose interval of 12 hours has also been used. Patients should be transferred to oral therapy as soon as possible. The use of the intramuscular route has been controversial because of concerns over safety and efficacy. However, some studies have shown that it can safely be used in adults and children with severe infections.[5-8] Intramuscular injections of quinine can be irritant and have caused pain, focal necrosis, and abscess formation; fatal tetanus has developed in some patients.[9] It has been suggested that some such reactions may be related to the use of preparations formulated in urethane or other irritant substances. Diluted solutions of quinine dihydrochloride 60 mg/mL adjusted to neutral pH appear to be less painful than the usual undiluted preparation of 300 mg/mL.

If facilities do not exist to give quinine parenterally then patients with severe malaria should receive quinine by mouth or nasogastric tube.

Quinine as formerly standardised used to contain a higher concentration of cinchona alkaloids and there might be synergy between mixtures of these alkaloids.[10] In practice no advantage has been shown by such mixtures over quinine alone in the treatment of chloroquine-resistant falciparum malaria.[11]

1. WHO. *WHO model formulary*. Geneva: WHO, 2004.
2. Molyneux M, Fox R. Diagnosis and treatment of malaria in Britain. *BMJ* 1993; **306:** 1175–80.
3. WHO. *Management of severe malaria: a practical handbook*. Geneva: WHO, 2000. Available at: http://www.who.int/malaria/docs/hbsm_toc.htm (accessed 16/07/07)
4. WHO. *Guidelines for the treatment of malaria*. Geneva: WHO, 2006. Also available at: http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf (accessed 05/06/06)
5. Wattanagoon Y, *et al.* Intramuscular loading dose of quinine for falciparum malaria: pharmacokinetics and toxicity. *BMJ* 1986; **293:** 11–13. Correction. *ibid.*; 362.
6. Mansor SM, *et al.* The safety and kinetics of intramuscular quinine in Malawian children with moderately severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 482–7.
7. Waller D, *et al.* The pharmacokinetic properties of intramuscular quinine in Gambian children with severe falciparum malaria. *Trans R Soc Trop Med Hyg* 1990; **84:** 488–91.
8. Schapira A, *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.
9. Yen LM, *et al.* Role of quinine in the high mortality of intramuscular injection tetanus. *Lancet* 1994; **344:** 786–7.
10. Druilhe P, *et al.* Activity of a combination of three cinchona bark alkaloids against Plasmodium falciparum in vitro. *Antimicrob Agents Chemother* 1988; **32:** 250–4.
11. Bunnag D, *et al.* A combination of quinine, quinidine and cinchonine (LA 40221) in the treatment of chloroquine resistant falciparum malaria in Thailand: two double-blind trials. *Trans R Soc Trop Med Hyg* 1989; **83:** 66.

Muscle spasm. Quinine (usually as quinine sulfate or bisulfate) has traditionally been used for nocturnal cramps (p.1887) but there has been concern over its efficacy and potential for adverse effects, especially in the elderly. In the USA, for example, the FDA ruled that quinine products should no longer be used for the management of nocturnal cramps.[1,2] A similar ban has been imposed in Australia.[3] Meta-analyses[4,5] concluded that although quinine was effective in the treatment of nocturnal cramps in ambulatory patients the risk of serious adverse effects should be borne in mind. It was recommended that patients should be closely monitored while the efficacy of quinine is assessed over a period of at least 4 weeks. Some[6] have recommended that treatment be stopped every 3 months to see whether it is still needed. Haemodialysis-induced cramp (p.1671) has been reported to respond to treatment with quinine[7,8] but similar concerns apply.

1. FDA. Drug products for the treatment and/or prevention of nocturnal leg muscle cramps for over-the-counter human use. *Fed Regist* 1994; **59:** 43234–52.
2. Nightingale SL. Quinine for nocturnal leg cramps. *ACP J Club* 1995; **123:** 86.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Quinine indications—cramps deleted. *Aust Adverse Drug React Bull* 2004; **23:** 20. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0410.htm (accessed 01/11/04)
4. Man-Son-Hing M, Wells G. Meta-analysis of efficacy of quinine for treatment of nocturnal leg cramps in elderly people. *BMJ* 1995; **310:** 13–17.
5. Man-Son-Hing M, *et al.* Quinine for nocturnal leg cramps: a meta-analysis including unpublished data. *J Gen Intern Med* 1998; **13:** 600–606.
6. Anonymous. Quinine for nocturnal leg cramps? *Drug Ther Bull* 1996; **34:** 7–8.
7. Kaji DM, *et al.* Prevention of muscle cramps in haemodialysis patients by quinine sulphate. *Lancet* 1976; **ii:** 66–7.
8. Roca AO, *et al.* Dialysis leg cramps; efficacy of quinine versus vitamin E. *ASAIO J* 1992; **38:** M481–M485.

Preparations

BP 2008: Quinine Bisulphate Tablets; Quinine Dihydrochloride Intravenous Infusion; Quinine Sulphate Tablets;
USP 31: Quinine Sulfate Capsules; Quinine Sulfate Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Circonyl; ***Austral.:*** Biquinate; Myoquin†; Quinate; Quinbisul; Quinoctal†; Quinsul; ***Braz.:*** Palukin; Paluquina†; ***Denm.:*** Kinin; ***Fr.:*** Quinoforme†; Surquina; ***Ger.:*** Limptar N; ***Gr.:*** Kinin†; ***India:*** Cinkona; Quinarsol; Quininga; ***NZ:*** Q200; Q300; ***Swed.:*** Kinin; ***Thai.:*** Genin; ***USA:*** Qualaquin.

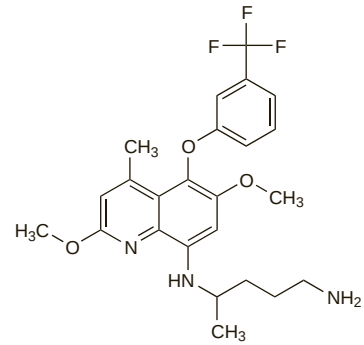
Multi-ingredient: ***Austria:*** Dilatol-Chinin; Iromin-Chinin-C; Limptar; Seltoc; ***Braz.:*** Monotrean; Monotrean B6; ***Fin.:*** Crampiton; Relapamil; ***Fr.:*** Dinacode†; Hexaquine; Okimus; Quinimax; ***Ger.:*** Limptar†; Togal Classic; ***Irl.:*** Anadin; ***Ital.:*** Monotrean†; ***Neth.:*** Aflukin C; ***NZ:*** Nicobrevin; ***Port.:*** Broncosil†; Rectopulmo Adultos†; ***Rus.:*** Analgin-Chinin (Анальгин-Хинин); ***S.Afr.:*** Ilvico; ***Spain:*** Brota Rectal Balsamico; ***UK:*** Nicobrevin.

Tafenoquine *(BAN, rINN)*

Tafenoquina; Tafénoquine; Tafenoquinum; WR-238605. (±)-8-[(4-Amino-1-methylbutyl)amino]-2,6-dimethoxy-4-methyl-5-[(α,α,α-trifluoro-*m*-tolyl)oxy]quinoline; (*RS*)-*N*⁴-[2,6-Dimethoxy-4-methyl-5-(3-trifluoromethylphenoxy)quinolin-8-yl]pentane-1,4-diamine.

Тафенохин

$C_{24}H_{28}F_3N_3O_3$ = 463.5.
CAS — 106635-80-7.



Profile

Tafenoquine is an 8-aminoquinoline antimalarial. It acts as a tissue schizontocide and is under investigation as the succinate for the radical cure and prevention of relapse in vivax malaria. It may also have a role in the prophylaxis of falciparum malaria.

◊ References.

1. Walsh DS, *et al.* Randomized dose-ranging study of the safety and efficacy of WR 238605 (tafenoquine) in the prevention of relapse of Plasmodium vivax malaria in Thailand. *J Infect Dis* 1999; **180:** 1282–7.
2. Lell B, *et al.* Malaria chemoprophylaxis with tafenoquine: a randomised study. *Lancet* 2000; **355:** 2041–5.
3. Shanks GD, *et al.* A new primaquine analogue, tafenoquine (WR 238605), for prophylaxis against Plasmodium falciparum malaria. *Clin Infect Dis* 2001; **33:** 1968–74.
4. Nasveld P, *et al.* Comparison of tafenoquine (WR238605) and primaquine in the post-exposure (terminal) prophylaxis of vivax malaria in Australian Defence Force personnel. *Trans R Soc Trop Med Hyg* 2002; **96:** 683–4.
5. Hale BR, *et al.* A randomized, double-blind, placebo-controlled, dose-ranging trial of tafenoquine for weekly prophylaxis against Plasmodium falciparum. *Clin Infect Dis* 2003; **36:** 541–9.
6. Walsh DS, *et al.* Randomized trial of 3-dose regimens of tafenoquine (WR238605) versus low-dose primaquine for preventing Plasmodium vivax malaria relapse. *Clin Infect Dis* 2004; **39:** 1095–1103.
7. Walsh DS, *et al.* Efficacy of monthly tafenoquine for prophylaxis of Plasmodium vivax and multidrug-resistant P. falciparum malaria. *J Infect Dis* 2004; **190:** 1456–63.