

THE USE OF ANTIMALARIAL DRUGS

Report of an Informal Consultation

World Health Organization, Geneva

WHO, 2001

Technical Review: A. Bosman, C. Delacolletta, P. Ojiambo, R. C. Ridley, A. Riestveld
R. Shrestha, A. Teklehaimanot

Text editor: S. Poole

Layout and production: WHO & Graficim

Cover photo courtesy of H. Anandén

The authors wish to recognize the contributions made to the writing of this report at country level by Ministers of Health and other partners, Regional Offices of WHO, and at a global level by mission reports, partners and the REM team.

Roll Back Malaria
World Health Organization
20, avenue Appia
CH-1211 Geneva 27, Switzerland
Tel: +(41) 22 791 3606, Fax: +(41) 22 791 4824,
E-mail: rbm@who.int
Web site: <http://www.rbm.who.int/>



WHO/CDS/REM/2001.11

© Copyright 2001 by Roll Back Malaria/World Health Organization

This document is not a formal publication of the World Health Organization and all rights are reserved by the organization. The document may, however, be freely reviewed, abstracted, reproduced or translated, in part or in whole, but not for sale nor for use in conjunction with commercial purposes.

The designation employed and the presentation of the material in this publication, including maps and tables do not imply the expression of any opinion whatsoever on the part of the secretariat of the World Health Organization concerning the legal status of any country, territory, city or area of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omission excepted, the names of proprietary products are distinguished by initial capital letters.

1. ANTIMALARIAL DRUGS IN CURRENT USE FOR MALARIA PREVENTION AND TREATMENT OF UNCOMPLICATED MALARIA

1.1 CHLOROQUINE

- Formulations**
- Tablets containing 100 mg or 150 mg of chloroquine base as phosphate or sulfate.
 - Syrup containing 50 mg of base as chloroquine phosphate or sulfate in 5 ml.

Efficacy Chloroquine is a 4-aminoquinoline that has marked and rapid schizonticidal activity against all infections of *P. malariae* and *P. ovale* and against chloroquine-sensitive infections of *P. falciparum* and *P. vivax*. It is also gametocytocidal against *P. vivax*, *P. malariae* and *P. ovale* as well as immature gametocytes (stages 1–3) of *P. falciparum*. It is not active against intrahepatic forms, and should therefore be used with primaquine to effect radical cure of *P. vivax* and *P. ovale*.

Use The use of chloroquine as a single first-line drug treatment is now increasingly limited following the evolution of chloroquine-resistant *P. falciparum*, but chloroquine remains the first-line drug of choice in most African countries south of the Sahara where acceptable clinical cure rates can be obtained. In areas where it is still used as a first-line drug, persistent parasitemia and lack of haematological recovery in children may be one of the early signs of chloroquine resistance. Even if the frequency of clinical failures is acceptable in the general population, a more effective first-line treatment may be required for vulnerable groups such as young children and pregnant women. However, the possible desirability of giving different drugs to different population groups must be balanced against logistic and acceptability problems.

In some areas chloroquine use could potentially be extended by its combination with other antimalarial drugs, in order to take continuing advantage of its antipyretic and anti-inflammatory effect and for its action against vivax malaria. This approach has been taken by East Timor, Ethiopia and Papua New Guinea where first-line therapy has been changed to chloroquine plus sulfadoxine–pyrimethamine where no laboratory diagnosis is available. In Uganda, where there is no *P. vivax*, the same combination has recently been advocated because some studies indicated higher efficacy compared with sulfadoxine–pyrimethamine alone.

Resistance of *P. vivax* to chloroquine was first documented in 1989 in Papua New Guinea and is now also confirmed in Indonesia and Myanmar (40, 68, 99–104). Such resistance has only been reported in areas where there is concurrent widespread resistance of *P. falciparum* to chloroquine. Well-documented chloroquine resistance has also been reported in South America (Brazil, Guatemala and Guyana) (41, 105). At present, the situation does not appear to require major changes in national treatment policies. However, it does

require continual monitoring since, in some areas of Indonesia and Papua New Guinea, 20–30% of patients infected with *P. vivax* have recurrences of parasitaemia 1–3 weeks after a course of 25 mg of chloroquine base per kg of body weight. Clinical attacks of chloroquine-resistant *P. vivax* can be treated with mefloquine or quinine.

Recommended treatment

Children and adults for whom the use of chloroquine is indicated, should receive a full treatment dose of 25 mg of chloroquine base per kg given over 3 days. The pharmacokinetically superior regimen consists of 10 mg of base per kg followed by 5 mg/kg 6–8 h later and 5 mg/kg on each of the following 2 days. A more practical regimen used in many areas consists of 10 mg/kg on the first and second days and 5 mg/kg on the third. Both these regimens provide a total dose of 25 mg/kg (e.g. 1 500 mg of base for a 60-kg adult). Details of the dosage schedules for all age groups and according to weight are given in Table 7.

There is no evidence to suggest that increasing the dosage will increase the clinical cure rate in such situations (106) and repeated administration of such high doses may produce adverse reactions.

Table 7. Dosage schedules for chloroquine treatment

Weight (kg)	Age (years)	Number of tablets					
		Tablets, 100 mg of base			Tablets, 150 mg of base		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5–6	< 4 months	0.5	0.5	0.5	0.5	0.25	0.25
7–10	4–11 months	1	1	0.5	0.5	0.5	0.5
11–14	1–2	1.5	1.5	0.5	1	1	0.5
15–18	3–4	2	2	0.5	1	1	1
19–24	5–7	2.5	2.5	1	1.5	1.5	1
25–35	8–10	3.5	3.5	2	2.5	2.5	1
36–50	11–13	5	5	2.5	3	3	2
50+	14+	6	6	3	4	4	2

Recommended chemoprophylaxis

- 5 mg of base per kg weekly in a single dose,
- or
- 10 mg of base per kg weekly, divided into 6 daily doses.

Chloroquine alone is recommended as a prophylactic drug in some of the areas where only *P. vivax* is present (Argentina, Iraq, Syria and Turkey; parts of Bolivia, China, Iran, Peru and Venezuela), or where *P. falciparum* is still sensitive to the drug (Central America north of the Panama Canal, Dominican Republic, Haiti, Tajikistan and parts of Ecuador).

Chloroquine may also be recommended in areas of moderate levels of *P. falciparum* resistance to chloroquine if combined with 200 mg of proguanil daily. This combination provides substantial protection, although less than mefloquine. This regimen is currently recommended for large parts of the Arabian Peninsula and Asia (but not South-East Asia), and in Mauritania, Namibia and part of Colombia.

Pharmacokinetic modelling indicates that the adult dose of 100 mg of chloroquine base daily may be superior to the weekly regimen (107), and a higher efficacy has been found in a retrospective study of travellers taking chloroquine only (108). However, there is a lack of evidence of higher efficacy from comparative studies of the daily compared with the weekly chloroquine regimen when combined with daily proguanil. The daily regimen results in a doubling of the total ingested dose of chloroquine compared with the weekly regimen, and is therefore less suitable for long-term travel because of the risk of adverse reactions (see below). In several countries a combination tablet containing 100 mg of chloroquine base plus 200 mg of proguanil hydrochloride is available, which may increase compliance in adults. Details of the single weekly doses of chloroquine for all age groups and according to weight are given in Table 8.

Table 8. Dosage schedules for chloroquine chemoprophylaxis

Weight (kg)	Age (years)	Number of tablets per week	
		Tablets, 100 mg of base	Tablets, 150 mg of base
5–6	< 4 months	0.25	0.25
7–10	4–11 months	0.5	0.5
11–14	1–2	0.75	0.5
15–18	3–4	1	0.75
19–24	5–7	1.25	1
25–35	8–10	2	1
36–50	11–13	2.5	2
50+	14+	3	2

Use in pregnancy

No abortifacient or teratogenic effects have been reported with chloroquine, so it may be considered safe for treatment or chemoprophylaxis of malaria during pregnancy (109). Although national antimalarial treatment policies in endemic countries may include recommendations for weekly chloroquine chemopro-

phylaxis throughout pregnancy to prevent malaria and its consequences in the pregnant woman and her developing fetus, adherence to this regimen has been very poor.

Drug disposition

Chloroquine is absorbed efficiently when administered orally, peak plasma concentrations being achieved within 3 h (range 2–12 h). The concentration reached in the plasma within 30 min after administration of a single dose of 10 mg/kg is usually substantially greater than the therapeutic level for chloroquine-sensitive *P. falciparum* parasites. The drug has a high capacity for binding to tissues, particularly the melanin-containing tissues of the skin and eye. Binding to plasma proteins, about 50%, is much less than expected from its extensive tissue binding. It is preferentially concentrated in erythrocytes and this concentration is enhanced in parasitized erythrocytes.

Chloroquine is metabolized slowly by de-ethylation of the side chain leading successively to monodesethyl- and bisdesethylchloroquine, followed by dealkylation. The antimalarial activity and pharmacokinetic profile of desethylchloroquine are similar to those of the parent drug. Chloroquine is eliminated slowly, the parent drug and its metabolites being detected in the blood for up to 56 days with an elimination half-life of around 10 days, depending on the sensitivity of the assay methods used. Chloroquine is predominantly excreted as the parent drug, desethylchloroquine accounting for only about 25% of the total drug excreted (11, 110).

Adverse effects

Serious adverse reactions to chloroquine are rare at the usual antimalarial dosages, but pruritus, which may be intolerable, is common among dark-skinned people. It can sometimes be alleviated by calamine lotion. As pruritus may compromise compliance, it is advisable to use an alternative effective and rapidly acting blood schizonticide in the event of reinfection.

Transient headaches, nausea, vomiting, gastrointestinal symptoms and "blurred vision" may also be experienced following chloroquine administration. This may be avoided by administering the dose after a meal. Attacks of acute porphyria and psoriasis may be precipitated in susceptible individuals. Very rarely adverse events include leukopenia, bleaching of the hair and, extremely rarely, aplastic blood and neurological disorders, such as polyneuritis, ototoxicity, seizures and neuromyopathy.

Irreversible visual impairment resulting from accumulation of chloroquine in the retina is a rare but recognized complication of long-term, high-dosage therapy. Cumulative total doses of 1 g of base per kg body weight or 50–100 g of base have been associated with retinal damage. Retinopathy has rarely, if ever, resulted from doses recommended for malaria chemoprophylaxis (109, 110). Twice-yearly screening for the detection of early retinal changes should be undertaken in anyone who has taken 300 mg of chloroquine weekly for over 5 years and requires further chemoprophylaxis. In travellers who have taken 100 mg daily, screening should be carried out after 3 years. If changes are observed, an alternative drug should be prescribed.

Contraindications

Chloroquine administration is contraindicated in persons:

- with known hypersensitivity,
- with a history of epilepsy,
- suffering from psoriasis.

Overdosage Chloroquine has a low safety margin. Acute chloroquine poisoning is extremely dangerous and death may occur within a few hours. Poisoning may result after oral ingestion by adults of a single amount of 1.5–2.0 g, i.e. 2–3 times the daily treatment dose. Symptoms include headache, nausea, diarrhoea, dizziness, muscular weakness and blurred vision, which may be dramatic with loss of vision. However, the main effect of overdosage is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, and death.

If the patient is seen within a few hours of the event, emesis must be induced or gastric lavage undertaken as rapidly as possible. If not, treatment is symptomatic and directed particularly to sustaining cardiovascular and respiratory function.

1.2 AMODIAQUINE

- Formulations**
- *Tablets containing 200 mg of amodiaquine base as hydrochloride or 153.1 mg of base as chlorohydrate.*
 - *Suspension containing 10 mg of amodiaquine base as hydrochloride or chlorohydrate per ml.*

Efficacy Amodiaquine is a 4-aminoquinoline antimalarial drug similar in structure and activity to chloroquine. Like chloroquine, it also possesses antipyretic and anti-inflammatory properties.

A systematic review of relevant studies on the treatment of uncomplicated falciparum malaria conducted over the past ten years in Africa showed that amodiaquine proved significantly more effective than chloroquine in clearing parasites, with a tendency for faster clinical recovery. This difference was also observed in areas with considerable chloroquine resistance (30, 111, 112). Data from Cameroon demonstrate better activity of 35 mg/kg than of 25 mg/kg in chloroquine-resistant malaria. However, there is no conclusive evidence that doses of > 25 mg/kg are associated with either improved efficacy or increased toxicity. Amodiaquine also exhibited faster fever clearance times than sulfadoxine–pyrimethamine although the two drugs were equally effective at parasite clearance by day 7, and sulfadoxine–pyrimethamine was more effective on days 14 and 28. This may be related to the slower antimalarial action of the combination and the antipyretic effect of amodiaquine (113, 114).