6 Nissen-Meyer R. Primary breast cancer: the effect of primary ovarian irradiation. *Ann Oncol* 1991; **2**: 343–46.
7 Nevinny HB, Nevinny D, Roscoff CB, Hall TC, Muench H. Prophylactic oophorectomy in breast cancer therapy. *Am J Surg* 1969; **117**: 531–36.
8 Ravdin RG, Lewison EF, Slack NH, et al. Results of a clinical trial concerning the worth of prophylactic oophorectomy for breast carcinoma. *Surg Gynecol Obstet* 1970; **31**: 1055–64.
9 Bryant AJS, Weir JA. Prophylactic oophorectomy in operable instances of carcinoma of the breast. *Surg Gynecol Obstet* 1981; **153**: 660–64.
10 Meakin JW, Hayward JL, Panzarella T, et al. Ovarian irradiation and prednisone therapy following surgery and radiotherapy for carcinoma of the breast. *Breast Cancer Res Treat* 1996; **37**: 11–19.
11 Ragaz J, Jackson S, Nilson K, et al. Randomized study of locoregional radiotherapy and ovarian ablation in premenopausal patients with breast cancer treated with adjuvant chemotherapy. *Proc Am Soc Clin Oncol* 1988; **7**: 12 (abstr).
12 Ludwig Breast Cancer Study Group. Chemotherapy with or without oophorectomy in high-risk premenopausal patients with operable breast cancer. *J Clin Oncol* 1985; **3**: 1059–67.
13 Richards MA, O'Reilly SM, Howell A, et al. Adjuvant cyclophosphamide, methotrexate and fluorouracil in patients with axillary node-positive breast cancer: an update of the Guy's/Manchester Trial. *J Clin Oncol* 1990; **8**: 2032–39.
14 Counsell CE, Clarke MJ, Slattery J, Sandercock PAG. The miracle of DICE therapy for acute stroke: fact or fictional product of subgroup analysis? *BMJ* 1994; **309**: 1677–81.
15 Scottish Cancer Trials Breast Group. Adjuvant ovarian ablation versus CMF chemotherapy in premenopausal women with pathological stage II breast carcinoma: the Scottish trial. *Lancet* 1993; **341**: 1293–98.
16 Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 1896; ii: 104–07.

Systematic review of amodiaquine treatment in uncomplicated malaria

P Olliaro, C Nevill, J LeBras, P Ringwald, P Mussano, P Garner, P Brasseur

Summary

Background Opinion and policy over the use of amodiaquine for treating malaria vary. Amodiaquine is more palatable than chloroquine and may be more effective but serious adverse events have been reported in travellers taking it as prophylaxis. It is not recommended as first-line treatment. In the light of the global debate over the use of this drug, we conducted a systematic review of the effectiveness and tolerability of amodiaquine in the treatment of uncomplicated falciparum malaria.

Methods This is a systematic review of published and unpublished randomised or pseudorandomised trials of amodiaquine. Observational reports were also systematically identified and reviewed to access evidence of serious adverse events.

Findings 40 trials met the inclusion criteria. Symptomatic patients were enrolled in 24 studies in comparisons of amodiaquine (n=1071) with chloroquine (n=1097). Amodiaquine was significantly more effective than chloroquine, with odds ratios and 99% confidence intervals (OR [99% CI]) of 4·29 (3·30–5·58) on day 7 and 6·00 (3·97–9·06) on day 14. Time to parasite clearance was significantly shorter with amodiaquine and fever clearance times were marginally faster. Eight studies compared amodiaquine with chloroquine in asymptomatic parasitaemia, with effects on parasitological outcomes similar to those for symptomatic malaria. At twelve sites, 692 amodiaquine and 679 sulfadoxine/pyrimethamine (S/P) recipients were enrolled. The two drugs did not differ significantly on day 7 (OR 0·74 [0·48–1·15]) but the odds ratios favoured S/P on day 14 (OR 0·51 [0·28–0·93]) and on day 28 (OR 0·30 [0·16–0·55]). The time to parasitological clearance was similar in the two groups; fever clearance times were significantly shorter with amodiaquine. Tolerability was assessed for both comparative and non-comparative trials. The rates of adverse events in controlled trials were 10·7%, 8·8%, and 14·3% with amodiaquine, chloroquine, and S/P, respectively. No life-threatening adverse events and no significant shifts in laboratory indices were reported.

Interpretation This systematic review of published and unpublished trials supports the use of amodiaquine in the treatment of uncomplicated malaria. However, there is partial cross-resistance between chloroquine and amodiaquine, and monitoring of the effectiveness of this drug and surveillance for evidence of toxicity must continue.

Lancet 1996; **348**: 1196–201
See Commentary page 1184

Introduction

Amodiaquine is a 4-aminoquinoline used widely in the past to treat and prevent malaria. In the mid-1980s, reports of fatal adverse drug reactions (ADRs) were described in travellers using amodiaquine as prophylaxis.[1,2] As a consequence one manufacturer (Parke-Davis) modified the labelling and withdrew prophylaxis as an indication, and in 1990 the World Health Organization (WHO) stopped using this drug in malaria control programmes.[3] WHO's 19th Expert Committee on Malaria modified this in 1993 to say that "amodiaquine could be used for treatment if the risk of infection outweighs the potential for [adverse drug reactions]", but still do not

UNDP/World Bank/WHO Special Programme for Training and Research in Tropical Diseases (TDR), Geneva, Switzerland (P Olliaro MD); **AMREF, Nairobi, Kenya** (C Nevill MD); **Institut de Médecine et d'Epidémiologie Tropicales, Hôpital Bichat-C Bernard, Paris, France** (J LeBras PhD); **ORSTOM/OCEAC, Yaoundé, Cameroon** (P Ringwald MD); **Cochrane Tropical Diseases Group, Liverpool, UK** (P Mussano PhD, P Garner MD); **and Laboratoire de Parasitologie, Hôpital C Nicolle, Rouen, France** (P Brasseur MD)

Correspondence to: Dr P Olliaro, CHEMAL, UNDP/World Bank/WHO Special Programme for Training and Research in Tropical Diseases (TDR), World Health Organization, 20 avenue Appia, 1211 Geneva 27, Switzerland

recommend amodiaquine as first-line treatment.[4] These statements have caused considerable confusion; several countries have banned amodiaquine whilst others have continued to use it as second or first line treatment for uncomplicated malaria.

The drug may have advantages over chloroquine: it may retain its efficacy in some areas of Africa where there is chloroquine resistance; it is more palatable and therefore easier to administer to children; and itching may be less with amodiaquine treatment. Most reports of toxicity have been with prophylactic rather than therapeutic use. It has also been suggested that amodiaquine may be a less toxic alternative to pyrimethamine/sulfadoxine (S/P) in HIV infected patients in sub-Saharan Africa.[5] Moreover, amodiaquine is widely available and some countries have local facilities to produce it; it is also the cheapest antimalarial drug after chloroquine. The global debate over the use of this drug prompted us to do a systematic review of the effectiveness and tolerability of amodiaquine in the treatment of uncomplicated falciparum malaria.

Materials and methods

Inclusion criteria and search strategy

Inclusion criteria were predetermined in terms of participants (adults or children with uncomplicated falciparum malaria or asymptomatic *Plasmodium falciparum* parasitaemia); of interventions (treatment with amodiaquine in randomised and alternate allocation comparisons with other treatment regimens); and of outcomes (parasitological conversion, parasite clearance time, fever clearance time). Any reported tolerability indices or adverse reactions were also extracted.

The search strategy involved an electronic search on MEDLINE, a search of the Cochrane Tropical Diseases Group trials register (which covers 25 journals, three in French),[6] and seeking unpublished and raw data from researchers and drug companies.

Efficacy

All identified trials were entered into a trial register. The inclusion criteria were then applied to trials separately by three people, and trials qualifying for analyses were retained. The quality of each included trial was assessed with respect to the adequacy of concealment, allocation procedures, blinding, and follow-up quality, using the standard protocol of the Cochrane Tropical Diseases Group.[6] Wherever possible, original data were obtained and analyses of individual patient data using the prespecified outcome measures were done. To minimise selection bias and the effect of patient attrition, the proportion of parasitological success was calculated from the total number of patients reportedly "evaluable" on day 7, 14, and 28. "Success" was a patient who was assessed and had a negative smear; "failures" were patients who were assessed and had a positive smear or were lost to follow-up. The odds ratio and 95% confidence intervals (OR, 95% CI) were calculated for individual studies meeting the inclusion criteria and these are that CIs used in individual lines in figures 1 and 2. The Cochrane Collaboration prefers 99% CIs and these are the intervals used for subtotal ORs in figures 1 and 2 and in the rest of this article. Pooled estimates of effectiveness were calculated from a weighted average, weight being based on the inverse of the variance.[7]

Time to parasitological clearance was calculated for individual studies and on the pooled data using the Kaplan-Meier procedure. Depending on the available time-points for analysis, two pools of data were created for trials using chloroquine as the comparator drug: pool A with six time-points (days 0, 1, 2, 3, 5, and 7) and pool B with assessments on days 0, 1, 2, and 7. For trials of amodiaquine compared with S/P, five data points (days 0, 1, 2, 3, and 7) were used. The log-rank test was used to compare the results of the amodiaquine and the comparator arm. In this analysis, in which all patients with a baseline positive smear were considered, achievement of parasite clearance was preferred to parasite clearance time as reported in the published papers because time to clearance is restricted to those patients who were, eventually, cleared of parasites. Weighted mean differences with lower and upper confidence limits were used for analysing fever clearance time (FCT).[8]

Comparison	Day	Studies	Success/no treated (%)		OR (95% CI)
			Amodiaquine	Comparator	
Chloroquine	7	24	890/1071 (83·1)	614/1097 (56·0)	4·29 (3·30–5·58)
	14	9	390/444 (87·8)	250/447 (55·9)	6·00 (3·97–9·06)
S/P	7	12	588/692 (85·0)	598/679 (88·1)	0·74 (0·48–1·15)
	14	6	267/325 (82·2)	303/343 (89·8)	0·51 (0·28–0·93)
	28	4	134/212 (63·2)	154/180 (85·6)	0·30 (0·16–0·55)

*Odds ratio for amodiaquine:comparator.

Table 1: **Parasitological success of amodiaquine compared with chloroquine or with S/P in symptomatic malaria**

Tolerability

An additional search was conducted to identify studies without control groups reporting adverse reactions. Data from trials included in the effectiveness review, as well as trials excluded because they did not meet inclusion criteria, were scrutinised for safety data. Only trials which specifically mentioned tolerability measures were considered, and all outcomes that could be interpreted as reflecting tolerability were summarised. Reports of adverse events were also sought from the WHO Collaborating Centre for International Drug Monitoring and from the Parke-Davis database.

Results

72 studies between 1983 and 1995 were identified, of which 40 (37 from Africa) met the inclusion criteria. 17 of the 40 were published, 5 were unpublished, and 18 were in the form of raw data (these studies include published articles for which individual patient data were made available by the trialist and Parke-Davis). Individual patient data accounted for about one-third of total amodiaquine patients in the comparison with chloroquine and more than half of those comparing amodiaquine with S/P. Amodiaquine was administered at doses ranging from 15·6 to 35 mg/kg over three days. Full details of location, participants, methods, and drug regimens of the 40 trials are available on the Cochrane database.[8*]

Trial quality was assessed, starting with allocation concealment.[9] Of the 40 studies, allocation was adequately concealed in three, and either not clearly described or unconcealed in 37. Except for one trial in the Philippines and one in China, no study was blinded. Six trials specified the method of generating the sequence, 22 mentioned randomisation but were not specific about the method, and 12 used methods that appeared to be unbiased. Nine studies used an intention-to-treat analysis with few losses to follow-up; eight trials report exclusions with levels of less than 10%; in the remaining 23, there was either no reporting of exclusions or exclusions were greater than 10%. Quality of number generation and analysis was better in the three trials with adequate concealment of allocation. Eight trials scored low on all three indices of quality. Diagnostic procedures varied with centres, although in most of them patients were admitted on the basis of thick and thin blood film results. No quality control of slide reading was mentioned in any of the studies. In 11 studies in Kenya, 10% of slides were systematically checked by a distant observer blind to the original results.

*A list of the 40 studies is obtainable from *The Lancet*

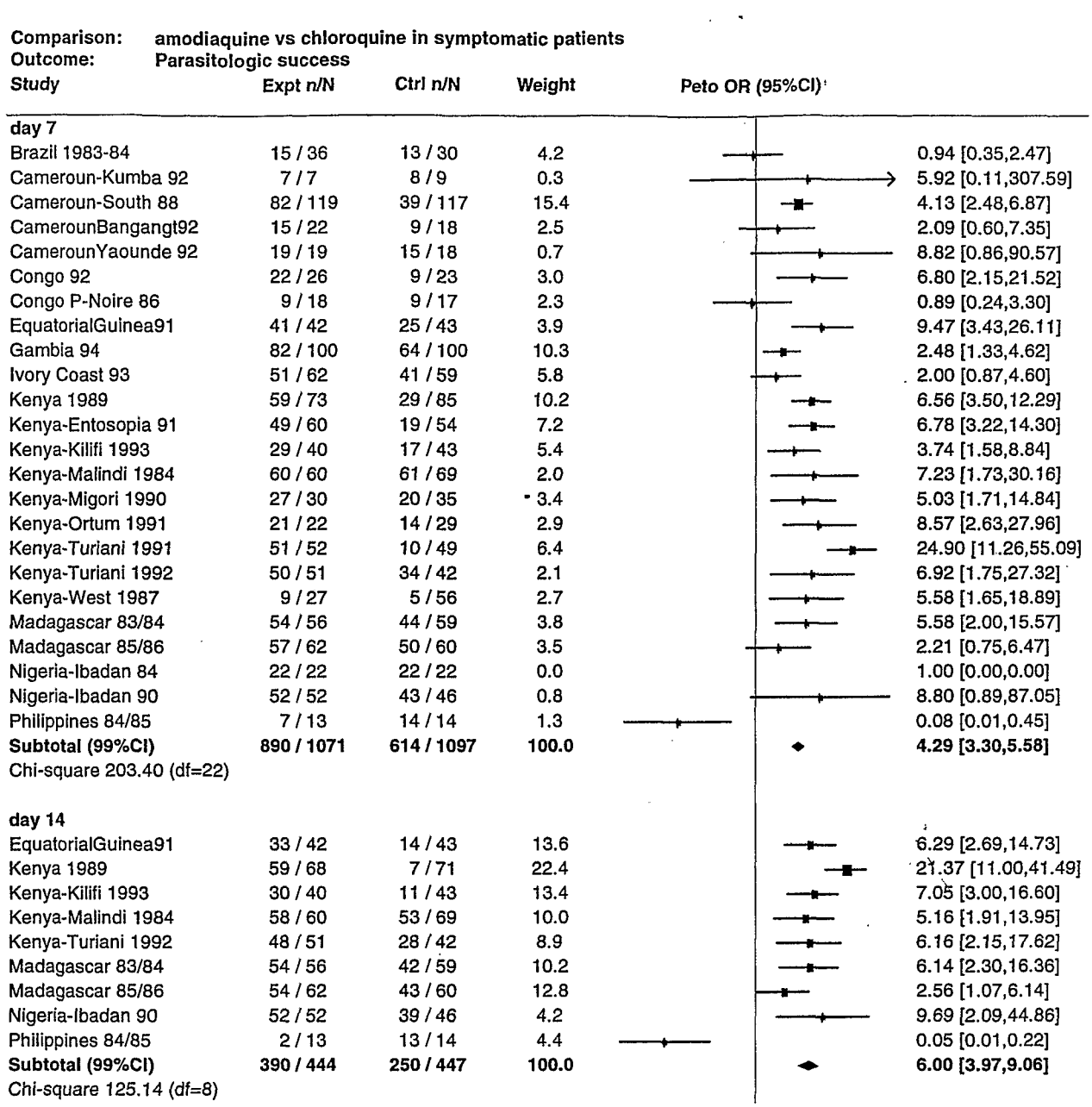

Figure 1: **Trials comparing amodiaquine and chloroquine in symptomatic patients**
Parasitological success (n) at day 7 and day 14 in total patients treated (N).

Amodiaquine versus *chloroquine*

Symptomatic uncomplicated falciparum malaria. 1071 patients received amodiaquine and 1097 chloroquine with studies at 24 slides, of which 22 were from Africa (accounting for 96% of the amodiaquine patients; 39% from Kenya, 16% from Cameroon). In this analysis patients with a positive smear or no data on day 7 were deemed failures. Amodiaquine was significantly more effective than chloroquine on day 7 (parasitological success rates 83% and 56%, respectively); the OR was 4·29 (99% CI 3·30–5·58). Few studies followed patients up to day 14 (444 amodiaquine, 447 chloroquine); nonetheless the parasitological success rates remained significantly different at 88% and 56%, respectively (OR 6·00 [3·97–9·06]) (table 1, figure 1). Because patients were not available for follow-up at day 14 were simply excluded, ORs for day 7 and day 14 should not be directly compared. Time to parasite clearance (day 0 through 7) was significantly shorter with amodiaquine than chloroquine whether the analysis used six or four data points (log-rank p=0·0025 and 0·0001, respectively) (table 2). Fever clearance (FCT) tended to be more rapid with amodiaquine (n=242) compared with chloroquine (n=230) in the four studies where it as reported, but the difference was not significant (weighted mean difference 146 min [99% CI −49 to +371).

Asymptomatic malaria parasitaemia. 488 amodiaquine recipients were compared with 482 chloroquine controls in eight studies. The success rate on day 7 was significantly higher for amodiaquine (91% *vs* 76%; OR=3·32 [99% CI 2·07–5·32]).

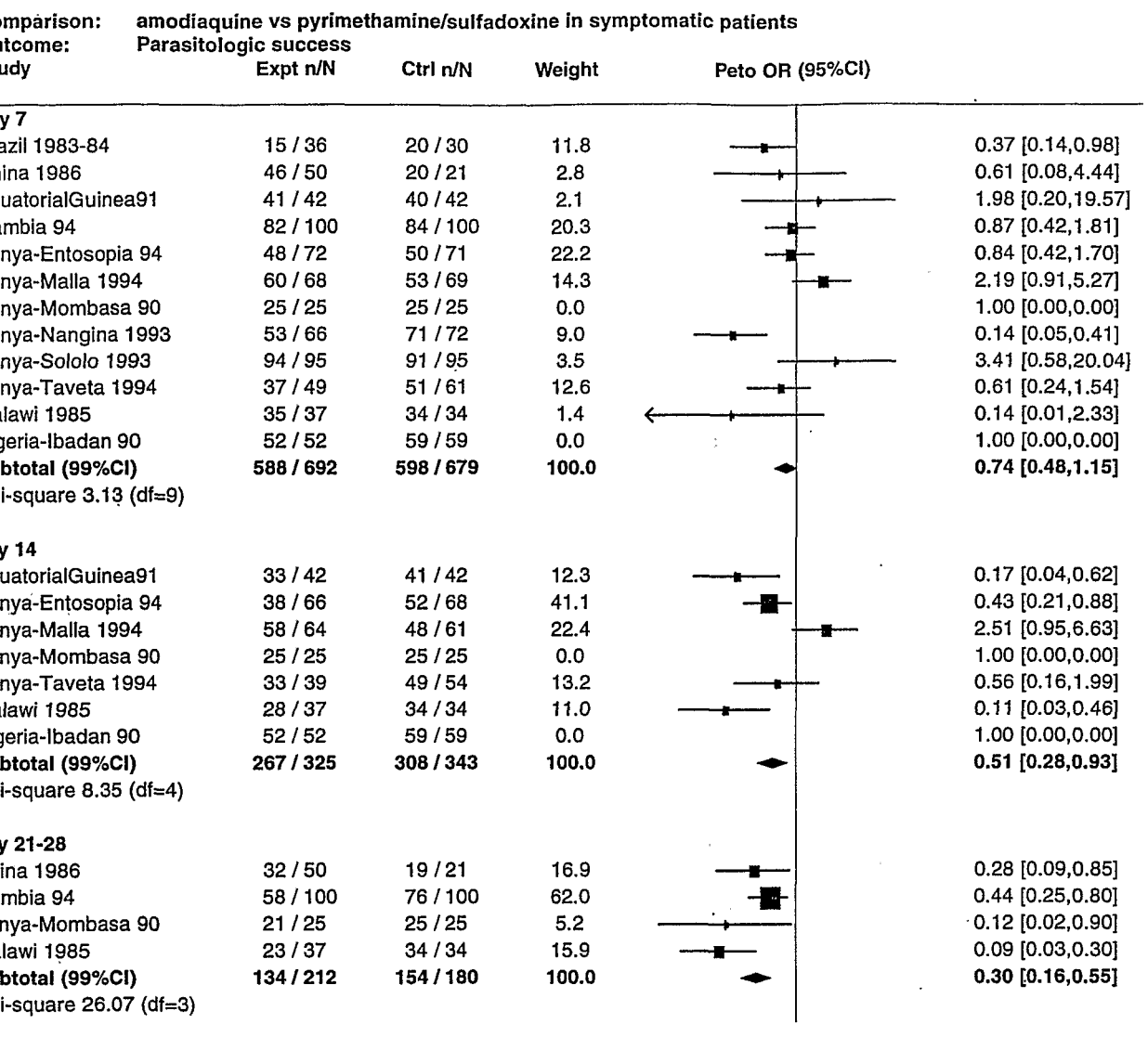

Figure 2: **Trials comparing amodiaquine and pyrimethamine/sulfadoxine in symptomatic patients**
Parasitological success (n) at day 7, day 14, or day 21–28 in total patients treated (N).

Amodiaquine versus *S/P*

Symptomatic uncomplicated falciparum malaria. Studies were done at 12 sites (10 from Africa) with 692 amodiaquine and 679 S/P recipients. Four studies also had a chloroquine arm. On day 7 the success rates were 85% with amodiaquine and 88% with S/P (OR=0·74 [99% CI 0·48–1·15]). 325 and 343 patients were evaluable at day 14, respectively, and 212 and 180 on day 28. The OR became significant by day 14 in favour of S/P (success rates 82·2% and 89·8%; OR=0·51 [99% CI 0·28–0·93]), and more strongly so by day 28 (63·2% and 85·6%; OR=0·30 [0·16–0·55]) (table 1, figure 2). The time to parasitological clearance (day 0 to 7) was similar in the two groups (log-rank p=0·27, table 2). FCTs (reported in five trials on 290 and 281 amodiaquine and S/P patients, respectively) were shorter with amodiaquine, the weighted mean difference being 15·5 h (99% CI −11·3 to −19·8 h).

Asymptomatic malaria parasitaemia. Two studies included in the eight studies of amodiaquine and chloroquine in asymptomatic *P falciparum*-infected patients also had a S/P arm. Those two enrolled 143 amodiaquine and 122 S/P recipients, with success rates on day 7 of 93% and 99%, respectively.

Data points (days)	Treatment	Total	Success (%)	Censored (%)	Log-rank p
0,1,2,3,5,7	ADQ	*108*	*99 (91·6)*	*9 (8·3)*	0·0025
	CLQ	109	78 (71·6)	31 (28·4)	
0,1,2,7	ADQ	*519*	*478 (92·1)*	*41 (7·9)*	0·0001
	CLQ	509	307 (60·3)	202 (39·7)	
01,2,3,7	ADQ	*424*	*385 (90·8)*	*39 (9·2)*	0·27
	S/P	451	401 (88·9)	50 (11·1)	

Table 2: **Time to parasite clearance**

Comparison	Studies	Patients with adverse events/ no treated (%)		OR (95% CI)
		Amodiaquine*	Comparator	
Chloroquine	8	33/143 (8)	36/411 (8·8)	0·85 (0·43–1·67)
S/P	3	33/127 (26)	15/105 (14·3)	1·68 (0·67–4·21)

*Total number of patients with adverse events on amodiaquine 52/488 (10·7%) due to patients enrolled in three-arm studies with both chloroquine and S/P.

Table 3: **Adverse events from trials**

Tolerability

From the trials that met the inclusion criteria for the effectiveness analyses, only 10 reported some evidence of tolerability assessment, accounting for 488 amodiaquine, 411 chloroquine, and 105 S/P patients. Adverse events were reported for 52 amodiaquine patients (10·7%), 36 on chloroquine (8·8%), and 15 on S/P (14·3%). No significant difference was observed between amodiaquine and chloroquine or S/P (table 3). The most commonly reported adverse events with amodiaquine were gastrointestinal (nausea and vomiting) and pruritus. No association was found between amodiaquine dose and incidence of adverse events. Those reported were of minor or moderate severity, and no severe, life-threatening adverse drug reaction was reported for amodiaquine.

A complete biochemical and haematological evaluation was performed for the 62 amodiaquine and 59 chloroquine patients in a study in Ivory Coast. No difference was observed between the two groups. Neutrophil counts on thick smear were available for 191 amodiaquine, 22 chloroquine, and 116 S/P recipients from Kenya (C Nevill, unpublished). Paired observations of neutrophil counts on day 14 versus baseline values of Ivory Coast and Kenya patients showed no significant change; the indices were remarkably similar with the three drugs.

24 non-comparative or non-randomised studies were identified, three of which, accounting for 776 amodiaquine recipients, reported 450 mild adverse events in 219 patients (28%). In one study in Cameroun, liver function tests were tested in 50 patients before and after treatment, with no significant change. In a recent study comparing amodiaquine with atovaquone plus proguanil, pruritus (in 27/63 patients), insomnia, dizziness, and weakness occurred more frequently on amodiaquine, while nausea and abdominal pain were more common with atovaquone plus proguanil. No significant shift in haematological and biochemical indices was detected.[10]

Data from two other possibly overlapping data sources were also made available. 115 adverse events were reported for 66 patients to the WHO Collaborating Centre for International Drug Monitoring during 1970–94 (M Pettersson, personal communication). These data are transmitted to the WHO Collaborating Centre by national drug regulatory authorities. The data are not checked at country level and information is often incomplete but this remains an important compilation of routine data. The most commonly affected body system was "WBCs and RES" (white blood cells and reticuloendothelial system). There were 28 reports, including 17 cases of agranulocytosis and 7 of granulocytopenia. The other body systems affected included liver and biliary system (n=21), skin and appendages (n=10), and body as a whole (n=9, including two deaths). Agranulocytosis and granulocytopenia affected adults of both sexes who had been on amodiaquine for an average of 9 weeks (range 3–360 days). In cases of agranulocytosis, time to onset varied from 48 to 98 days in seven of these cases; the other 10 had no dates filled in. Reasons for amodiaquine administration were seldom reported. Drug-event relationship were reported as certain in one case, probable in 11, possible in 13, unlikely in two, and unknown in 39. Of the 66 patients 35 had recovered without sequelae at the time of reporting, two died due to adverse reactions, in one other death the drug may have been contributory, and 11 patients had not yet recovered; outcome was not recorded in the other 17.

Between 1985 and 1991 (Parke-Davis data on file), 42 cases of serious adverse effects were reported during amodiaquine prophylaxis. These were 28 cases of agranulocytosis (9 died) and 14 of hepatitis (3 died). Amodiaquine intake ranged between 200 and 700 mg per week for 3–48 weeks.

Discussion

Some of the methodological deficiencies in published and unpublished trials have inevitably led to a bias in these analyses. Most articles report data only on the patients deemed "evaluable" as per the protocol, usually those who completed the scheduled study period (7, 14, or 28 days). Because no details were given on the "eligible" patients, and those where treatment was prematurely discontinued or who were withdrawn or lost to follow-up, no true intent-to-treat analysis could be done. Obtaining raw data has partly rectified the problem, although a selection bias still remains in favour of sensitivity. In contrast, the criteria adopted in the analysis of efficacy (ie, the missing data counted as failures) will introduce a bias toward resistance. In fact, non-attendees were shown to do well in an ad-hoc study in Kenya (C Nevill, unpublished). The availability of data to reanalyse had led us to identify two populations—the "evaluable" patients and those actually assessed at each target visit. The denominator did not vary substantially though; nor did the level of significance of the comparisons in the sets of patients.

The data are mainly from eastern, central, and western Africa, and although representing a wide range of malaria epidemiological patterns and resistance patterns, care should be taken in applying these results elsewhere. In this review, amodiaquine was significantly more effective than chloroquine in clearing parasites in all analyses done, with a tendency also for a faster clinical recovery as tested by a marginal advantage for fever clearance time. With respect to S/P no difference in parasitological outcomes was observed within 7 days of study, while S/P showed superiority during longer-term follow-up. This finding is not unexpected in view of the long-half life of S/P. We do not know whether the difference observed is due to recrudescent parasites or to reinfections. An improvement in symptoms was apparent with amodiaquine, as has been reported previously, and this could be ascribed to the anti-inflammatory/antipyretic effect of the aminoquinolines.

Amodiaquine seems to be no more toxic than chloroquine or S/P when administered at doses up to 35 mg/kg total dose over three days for treating adult and children with uncomplicated falciparum malaria. Under these conditions of use, and within the limitations of the sample size, no severe, life-threatening, or fatal adverse reaction occurred.

After oral intake, amodiaquine is rapidly and extensively metabolised to an active metabolite, desethylamodiaquine; both amodiaquine and desethylamodiaquine are chemically unstable in aqueous solution, undergoing transformation to a protein-arylating quinone imine.[11] The mechanism of toxicity of amodiaquine seems not to be related to direct toxicity of the parent compound or metabolites in bone marrow cell precursors,[12] but rather to the immunogenic properties of the quinone imine.[13,14] It is still unclear why, with most people exposed having anti-drug antibody, so few would have organ-specific toxicity.

So far, serious and life-threatening adverse drug reactions have been described only during prophylaxis.

Based on reported rates, the risk of serious reactions associated with the prophylactic use of amodiaquine can be estimated at 1 in every 2100 treatments for agranulocytosis, 1 in 15 500 for hepatoxicity, and 1 in 30 000 for aplastic anaemia, with a total case fatality rate of 1 in 15 650[15] (P A Phillips-Howard, personal communication). The risk of fatal adverse reactions to amodiaquine is similar to that to S/P.

Amodiaquine treatment appears to be safer than amodiaquine prophylaxis. In the 14 cases of agranulocytosis and/or hepatitis reported[1,2] the mean (SD) total dose of amodiaquine was 3·44 (1·2) g over 7·7 (2·3) weeks, corresponding to 2·3 times the dose of 1·5 g for a 60 kg individual. Treatment starts to resemble prophylaxis in areas where malaria is hyperendemic, where individuals receive several malaria treatments per year. Yet very few side-effects of amodiaquine treatment are reported. Although this review cannot dispel fear of amodiaquine toxicity with repeat treatments (that mimic prophylaxis) the slow "antipyretic" action of S/P, as well as its decreasing efficacy, appears to encourage multiple dose regimens with a similar level of risk.

This review has collated convincing evidence that amodiaquine is superior to chloroquine, and that applies to areas with considerable chloroquine resistance. There is a role for amodiaquine where chloroquine resistance is present although that role may be curtailed by partial amodiaquine cross-resistance with chloroquine. The comparison with S/P is potentially more important in view of the value of low-cost antimalarial drugs and the concerns around the useful life of sulpha drugs with long half-lives now that they are so widely used in sub-Saharan Africa. The faster symptomatic recovery with amodiaquine would avoid the need to give antipyretics, as is usual with S/P. The longer protection induced by S/P may also prove more of a hazard long-term since it could encourage the selection of resistant parasites.

This review is the most comprehensive attempt to date to identify all published and unpublished trials. Another review using a different methodology (A Rietveld and P Trigg, unpublished) also judged that the WHO recommendation to stop using amodiaquine in malaria control programmes for treatment was more prudent than practical, especially since so few affordable alternatives are available. When chloroquine, amodiaquine, and S/P are no longer effective, the next antimalarial drugs in line cost 7–60 times as much. (A Rietveld, personal communication), placing a full treatment course out of the reach of many patients. The review supports the continued use of amodiaquine in the treatment of uncomplicated malaria. Partial cross-resistance between chloroquine and amodiaquine should be borne in mind, however, and both monitoring of effectiveness and surveillance for evidence of toxicity must be maintained.

This review was made possible by researchers who kindly provided data and made comments, and include B Greenwood and O Müller (The Gambia), L Salako (Nigeria), A Shapira (WHO, Vietnam), and B Dubois (Parke-Davis, France). Data on amodiaquine adverse events were kindly provided by M Petersson (WHO Collaborating Centre, Sweden). Others who have helped with specialist advice include A Rietveld and V Mattei (WHO, Switzerland), J Portal (Parke-Davis, France), P Winstanley (UK), A Oxman (Denmark), A Herxheimer (UK). Elements of an unpublished WHO study by A Rietveld and P Trigg were also used. This review was conducted as an activity of the Cochrane Tropical Diseases Group, supported by a grant from the Overseas Development Administration (UK), and of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

References

1 Hatton C, Peto T, Bunch C, Pasvol G, Russel S, Singer C, Edwards G, Winstanley P. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986; i: 411–13.
2 Neftel K, Woodly W, Schmidt R, Frich P, Fehr J. Amodiaquine to induced agranulocytosis and liver damage. *BMJ* 1986; **292:** 721–23.
3 World Health Organization. Practical chemotherapy of malaria: report of a WHO scientific group. *Tech Rep Ser WHO* 1990, no 805.
4 World Health Organisation 19th Expert Committee on Malaria. Report. Geneva: WHO, 1993.
5 Coopman SA, Johnson RA, Platt R, Stern RS. Cutaneous disease and drug reaction in HIV infection. *N Engl J Med* 1993; **328:** 1670–74.
6 Garner P, Gelband H, Olliaro P, Salinas R, Wilkinson D, eds. Tropical diseases module of the Cochrane Database of Systematic Reviews (updated Oct 7, 1996). Available in The Cochrane Library (database on disk and CD-ROM). The Cochrane Collaboration; Issue 3. Oxford: Update Software; 1996. Updated quarterly. Available from: BMJ Publishing Group.
7 Early Breast Cancer Trialists' Collaborative Group. Statistical methods. In: Treatment of early breast cancer: vol I, worldwide evidence 1985–1990. Oxford: Oxford University Press, 1990: 13–18.
8 Olliaro P, Mussano P. Efficacy and safety of amodiaquine for the tretment of malaria. In: Garner P, Gelband H, Olliaro P, Salinas R, Wilkinson D, eds. Tropical diseases module of the Cochrane Database of Systematic Reviews (updated Oct 7, 1996).
9 Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995; **273:** 408–12.
10 Radloff PD, Phillips J, Nkeeyi M, Hutchinson D, Kremsner PG. Atovaquone and proguanil for *Plasmodium falciparum* malaria. *Lancet* 1996; **347:** 1511–13.
11 Maggs JL, Tingle MD, Kitteringham NR, Parke BK. Mechanisms of formation of protein to arylating intermediaries from amodiaquine, a myelotoxin and hepatotoxin in man. *Biochem Pharmacol* 1988; **37:** 305–11.
12 Winstanley PA, Coleman JW, Maggs JL, Breckenridge AM, Park BK. The toxicity of amodiaquine and its principal metabolites towards mononuclear leucocytes and granulocyte/monocyte colony forming units. *Br J Clin Pharmacol* 1990; **29:** 479–85.
13 Clarke JB, et al. Immunogenicity of amodiaquine in the rat. *Int Arch Allergy Appl Immunol* 1990; **91:** 335–42.
14 Clarke JB, Naftel K, Kitteringham NR, Park BK. Detection of antidrug IgG antibodies in patients with adverse drug reactions to amodiaquine. *Int Arch Allergy Appl Immunol* 1991; **5:** 369–75.
15 Phillips-Howard PA, West LJ. Serious adverse drug reactions to pyrimethamine—sulfadoxine, pyrimethamine—dapsone and amodiaquine in Britain. *J R Soc Med* 1990; **83:** 82–85.

THE LANCET

Volume 348, Number 9036 • Founded 1823 • Published weekly • Saturday 2 November 1996

£3.50