Quinine monotherapy for treating uncomplicated malaria in the era of artemisinin-based combination therapy: an appropriate public health policy?

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Several African countries that have adopted artemisinin-based combination therapy (ACT) as first-line treatment of uncomplicated *Plasmodium falciparum* malaria also use quinine monotherapy as second-line therapy. This policy goes against WHO recommendations for combination therapy and could be considered an inappropriate public health policy. Adherence to a 7-day quinine treatment schedule is likely to be poor and may increase the risk of selecting resistant parasites. Furthermore, because quinine has limited post-treatment prophylaxis, it will not prevent, in areas of intense transmission, recurrent malaria infections, which can lead to additional morbidity, including anaemia. Therefore, ACTs and not quinine should be used as second-line treatment, because these are well tolerated, highly efficacious, and have the advantage of reducing gametocyte carriage and consequently malaria transmissibility, particularly in areas of less intense transmission.

Introduction

The treatment of uncomplicated malaria in endemic countries has undergone dramatic changes in response to the increasing resistance to commonly used monotherapies, specifically chloroquine, amodiaquine, and sulfadoxine–pyrimethamine. As a response to the widespread antimalarial drug resistance to chloroquine and sulfadoxine–pyrimethamine, WHO recommends combination therapies, preferably those containing an artemisinin derivative (artemisinin-based combination therapy [ACT]).[1]

An increasing number of countries have adopted ACT as first-line treatment for *Plasmodium falciparum* malaria (figure, table). By the end of 2006, 66 countries in the African, southeast Asian, and western Pacific regions of WHO had adopted ACT.[2] National antimalarial drug policies normally recommend at least two standard treatment regimens for uncomplicated *P falciparum* malaria: a first-line treatment for routine use, and a second-line alternative if the former treatment has failed, is contraindicated (in pregnancy or history of allergic reaction), or is not available.[3,4]

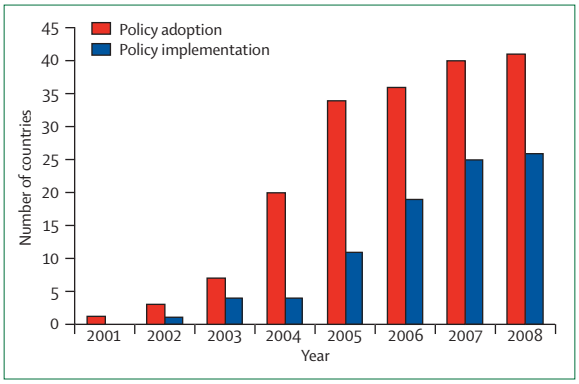

Figure: **Policy adoption and implementation of artemisinin-based combination therapy in WHO African region**
Data from WHO.[2]

Medicines recommended by WHO for second-line treatments include, in order of preference, an alternative ACT known to be effective in the region, artesunate plus tetracycline or doxycycline or clindamycin, and quinine plus tetracycline or doxycycline or clindamycin.[1] However, despite these guidelines, the treatment policies of 29 African countries recommend oral quinine monotherapy as the second-line regimen (table).[5,6]

Brief overview of quinine

Quinine is an aryl aminoalcohol and has a similar structure to quinidine, chloroquine, amodiaquine, mefloquine, halofantrine, lumefantrine, piperaquine, and tafenoquine. The chemical structural similarities between quinine and these other medicines vary from close to distant. Quinine originates from the bark of a tree, *Cinchona officinalis*, which is native to South America. The bark was named cinchona in 1742 by Linnaeus and was used extensively as a remedy for fever. It was brought by Jesuit fathers to Europe, where it was called "Jesuit powder/bark". In 1820, two French chemists isolated quinine from cinchona bark, and quinine became the treatment of choice for intermittent fever throughout the world.[7] Parenteral quinine, artesunate, and artemether are currently the only three medicines recommended by WHO for treating severe *P falciparum* malaria.[1] In areas of low transmission or outside malaria endemic areas, intravenous or intramuscular artesunate is the drug of choice. However, insufficient evidence exists for its use in high-transmission settings and either parenteral artesunate, quinine, or artemether should be used instead.

Tolerability

Oral quinine has marked side-effects, including tinnitus, dizziness, and nausea. The standard daily dosage of 30 mg/kg bodyweight administered in three divided doses every 8 h is often associated with cinchonism, a constellation of minor but unpleasant adverse effects

consisting of nausea, headache, tinnitus, high-tone hearing impairment, and blurred vision. Even more unpleasant symptoms such as vomiting, abdominal pain, diarrhoea, and vertigo may occur.[8] The high incidence of side-effects is likely to negatively influence adherence to the prescribed treatment and may contribute to its premature termination.[9]

Efficacy

Despite widespread use of quinine for treating malaria in pregnancy and as a second-line regimen for treating uncomplicated malaria, very few countries routinely monitor its efficacy, as recommended by WHO for any first-line and second-line regimen, and data on its efficacy are thus limited. The treatment schedule generally recommended for quinine in sub-Saharan Africa is a dose of 10 mg/kg bodyweight given every 8 h for 1 week. However, there is no evidence that this has achieved an acceptable effectiveness as second-line treatment.[1] In-vitro studies have shown decreased sensitivity to quinine in more than 50% of *P falciparum* infections in areas of southeast Asia, and similar observations have been made in Africa.[10,11] In a study in the Sudan, in which 62 patients with uncomplicated *P falciparum* malaria were treated with oral quinine (10 mg/kg thrice daily for 7 days), 28-day quinine failure after PCR genotyping correction was 6·4%.[12] On the Thai–Burmese border, recrudescence at day 63, after 7 days of supervised quinine treatment in pregnant Karen women, was 33% (over the threshold recommended by WHO for a change in drug policy).[13] In Vietnam, a study comparing quinine versus artemisinin

	***Plasmodium falciparum* malaria**				***Plasmodium vivax* malaria**
	Uncomplicated	Second line	Severe malaria	During pregnancy	
Algeria	..	..	..	..	Chloroquine
Angola	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Benin	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Botswana	Artemether–lumefantrine*	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Burkina Faso	Artemether–lumefantrine*	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Burundi	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Cameroon	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine	..
Cape Verde	Chloroquine	Sulphadoxine–pyrimethamine	Quinine (7 days)	Quinine	..
Central African Republic	Artemether–lumefantrine*	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Chad	Artesunate plus amodiaquine* or artemether–lumefantrine*	Quinine (7 days)	Quinine (7 days)	Quinine	..
Comoros	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Congo	Artesunate plus amodiaquine*	Artemether–lumefantrine*	Quinine (7 days)	Quinine	..
Côte d'Ivoire	Artesunate plus amodiaquine*	Artemether–lumefantrine	Quinine (7 days)	Quinine	..
Democratic Republic of Congo	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine	..
Equatorial Guinea	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine	..
Eritrea	Chloroquine plus sulphadoxine–pyrimethamine	Quinine (7 days)	Quinine (7 days)	Quinine	Chloroquine plus primaquine
Ethiopia	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine	Chloroquine
Gabon	Artesunate plus amodiaquine	Artemether–lumefantrine	Quinine (7 days)	Quinine	..
Gambia	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine	..
Ghana	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine (artesunate plus amodiaquine in 2nd and 3rd trimester)	..
Guinea	Artesunate plus amodiaquine*	Quinine (7 days)	Quinine (7 days)	Quinine	..
Guinea-Bissau	Artemether–lumefantrine*	Quinine (7 days)	Quinine (7 days)	Quinine	..
Kenya	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (artemether–lumefantrine in 2nd and 3rd trimester)	..
Liberia	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine	..
Madagascar	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine	..
Malawi	Artemether–lumefantrine	Artesunate plus amodiaquine*	Quinine (7 days)	Sulphadoxine–pyrimethamine or quinine (7 days)	..
Mali	Artemether–lumefantrine*	Artesunate plus sulphadoxine–pyrimethamine	Quinine (7 days)	Quinine (7 days)	..
Mauritania	Artesunate plus amodiaquine*	..	Quinine (7 days)	..	..
Mauritius		..	Quinine (7 days)	..	Chloroquine
Mozambique	Artemether–lumefantrine*	Artesunate plus amodiaquine	Quinine (7 days)	Quinine	..

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	Plasmodium falciparum malaria				*Plasmodium vivax* malaria
	Uncomplicated	Second line	Severe malaria	During pregnancy	
(Continued from previous page)					
Namibia	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Niger	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	..	..
Nigeria	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (ACT in 2nd and 3rd trimester)	..
Rwanda	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	..	..
Sao Tome and Principe	Artesunate plus amodiaquine	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days) or artesunate plus amodiaquine	..
Senegal	Artesunate plus amodiaquine	..	Quinine (7 days)	Quinine	..
Sierra Leone	Artesunate plus amodiaquine	Quinine (7 days)	Quinine (7 days)	Quinine	..
South Africa (KwaZulu Natal)	..	Quinine plus chloroquine	Quinine (7 days)	Chloroquine plus proguanil	Quinine (7 days)
South Africa (Mpumalana)	Artemether–lumefantrine	Quinine plus chloroquine	Quinine (7 days)	Chloroquine plus proguanil	Quinine (7 days)
Swaziland	Chloroquine	Sulphadoxine–pyrimethamine	Quinine (7 days)	Quinine	..
Togo	Artemether–lumefantrine	..	Quinine (7 days)	..	..
Uganda	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (7 days)	..
Tanzania (mainland)	Artemether–lumefantrine	Quinine (ACT in 2nd and 3rd trimester)	Quinine (7 days)	Sulphadoxine–pyrimethamine (intermittent presumptive treatment)	Quinine (7 days)
Zambia	Artemether–lumefantrine	Quinine (7 days)	Quinine (7 days)	Quinine (ACT in 2nd and 3rd trimester)	..
Zimbabwe	Artemether–lumefantrine*	Quinine (7 days)	Quinine (7 days)	Quinine (ACT in 2nd and 3rd trimester)	..

ACT=Artemisinin-based combination therapy. *Policy adopted, not currently being deployed, implementation process ongoing.

Table: **Malaria treatment regimens in the WHO African region**

for treating uncomplicated malaria reported a risk of recrudescence of up to 16% after 7 days of follow-up.[14]

Most studies on quinine have assessed the efficacy of 3-day or 5-day short-course treatment, although most of them have not done PCR analyses to distinguish recrudescence from a new infection. Therefore, the estimation of the true efficacy requires taking into account the likely reinfection rate in the study area. A study on a 3-day oral regimen of quinine in an area of northern Nigeria reported that PCR-uncorrected failure at day 14 was 21%.[15] A systematic review showed 30–50% recurrent infections during 28 days of follow-up in patients receiving 3 days of quinine therapy.[9] After 5 days of quinine treatment, the risk of failure uncorrected by PCR observed in Equatorial Guinea was higher than 40%.[16]

Use of a different dosing scheme has not proved any better. A study done in the Democratic Republic of Congo (former Zaire) showed that 9% of the children given quinine once daily at a dose of 20 mg/kg bodyweight for 7 days failed to clear parasitaemia at day 7 compared with only 2% of those treated with a single dose of sulfadoxine-pyrimethamine.[17] In the same study, parasitaemia at day 14 was 26% in the quinine group versus 8% in children treated with sulfadoxine-pyrimethamine.[17]

Nevertheless, some studies have shown an extremely high efficacy of quinine. For example, in Gabon, the in-vitro sensitivity of *P falciparum* to quinine has remained quite high over the past 10 years.[18] Similarly, studies in Equatorial Guinea and Venezuela have shown very high efficacy for quinine after 28 days of follow-up.[19,20] Quinine resistance might not be a major concern in Africa, because despite having been used (and in some instances abused) for a long time, its 7-day course administered under direct observation has maintained good clinical efficacy. However, its effectiveness is likely to be suboptimum because of poor adherence to treatment in the absence of direct observation.

Adherence to treatment

Quinine treatment has substantial disadvantages mainly because of its poor tolerability and the long treatment course.[21] Day-28 effectiveness after the 7-day dosing scheme of oral quinine monotherapy among Gabonese pregnant women was only 60%, and this poor result was attributed to low adherence.[22] Quinine is also known to induce substantial side-effects, which are mostly experienced during the second half of the treatment course. These are due to reduced plasma binding in already convalescent, asymptomatic patients.[23,24] The unpleasant bitter taste of quinine tablets and the development of increasingly impeding side-effects in the absence of malaria-related symptoms might hamper patients' adherence with longer treatment durations.[22] Some studies have reported adherence to the 7-day quinine regimen to be as low as

71%.[25] However, a dosing scheme over 7 days is required for maximum cure. Consequently, poor adherence is associated with a high risk of treatment failure.

Use of quinine for uncomplicated malaria during pregnancy

Malaria in pregnancy is associated with unwanted consequences for the mother and fetus that include low birthweight, increased anaemia, and risk of severe malaria. The recommended antimalarial drugs for the first trimester of pregnancy are quinine plus clindamycin for 7 days. In the second and third trimesters of pregnancy, an ACT known to be effective in that particular country or region should be used. Alternatively, artesunate plus clindamycin or quinine plus clindamycin may be given for 7 days.[1] However, pregnant women often receive quinine monotherapy, with recrudescence as high as 35%.[13] The combination of quinine and clindamycin remains highly efficacious, but is not often available and affordable in most endemic countries.[13,22] Some potential alternatives exist, including artemether-lumefantrine, azithromycin, artesunate-mefloquine, or dihydro-artemisinin-piperaquine, but data on their safety, efficacy, and pharmacokinetics in pregnancy are scarce and urgently need to be collected.

Is quinine monotherapy justified?

Despite a few studies that show good quinine efficacy, we question the rationale for continuing its use as second-line treatment in the era of ACTs for the following reasons. First, the complicated quinine dosing scheme and poor tolerance is associated with poor adherence that results in recurrent attacks of malaria and anaemia. Second, the possible poor adherence to the quinine treatment schedule is likely to increase the risk of selecting quinine-resistant parasites. Third, antimalarial treatment policies should aim to offer both first-line and second-line treatments that are highly effective and that also reduce the risk of the emergence of resistance. We believe that oral quinine monotherapy does not serve any of the above purposes and suitable alternatives should be defined as a matter of urgency. In addition, effective treatment with drugs that have a longer post-treatment prophylaxis than quinine is likely to prevent recurrent malaria infections during the month after treatment, which should prevent additional morbidity associated with repeated infections. Finally, the continued use of quinine monotherapy as second-line treatment for recurrent infections, most of them uncomplicated cases, goes against the WHO recommendations of using combination treatment,[1] and therefore, quinine monotherapy for uncomplicated malaria cases could be considered to be an inappropriate public health policy.

Quinine monotherapy, if prescribed and used correctly, can cure malaria, and is currently the only drug recommended for the management of uncomplicated malaria in pregnant women in the first trimester. Quinine use in other situations should be based on a case-by-case assessment of the contraindications for the other available options. Therefore, a blanket public health policy that recommends the use of quinine as a second-line regimen is inappropriate.

ACT as second-line treatment

To have an effective second-line treatment and to decrease the risk of treatment failure, an alternative to quinine for second-line therapy is urgently needed. The suitable alternatives to quinine need to be defined and their efficacy and effectiveness tested. When treatment policies were changed from a recommendation of chloroquine or sulfadoxine-pyrimethamine to that of ACTs, there were few options for second-line treatment, and the use of quinine, despite being against all the best practices, could have been justified. However, the ACT landscape has changed dramatically over the past few years and several highly efficacious ACTs are now available; thus, there is no reason to prevent their use as second-line treatments.

Use of an alternative ACT as second-line treatment has several advantages. First, they are well tolerated and highly efficacious. According to the WHO *World Malaria Report*,[2] not a single failure at day 14 was detected in 4917 patients enrolled in 32 trials testing artemisinin or its derivatives. In seven other trials, failure at day 14 varied from 1% to 7%.[2] Second, ACTs have the advantages of simplicity of the dosing scheme, and are given over only 3 days instead of 7 days, possibly favouring adherence.[1] In addition, from a public health perspective, ACTs have the advantage of reducing gametocyte carriage and thus reduce the transmissibility of malaria,[26] particularly in areas of low endemicity.

ACT is currently accepted as the best option for treating uncomplicated malaria. However, the greatest challenge is to choose the most appropriate regimen for a given area, and to finance and organise its use.[27] Some concerns could arise with respect to the use of an alternative ACT as second-line treatment for malaria, including availability, high cost, potential for wastage, and uncertainties in supply. However, these factors should be weighed against the likely suboptimum effectiveness of quinine monotherapy. The decision to change a national drug policy is probably the easier part of a complex process. It should then be followed by the harmonisation of the various national treatment guidelines, effective in-service training, adequate drug supply, and education of the patient population.[6] In addition, monitoring the safety, efficacy, and effectiveness of quinine and ACTs when used as a first-line or second-line treatment is needed because several factors can contribute to treatment failure, including incorrect dosing, non-compliance with the duration of dosing, poor drug quality, drug interactions, poor or erratic absorption, and misdiagnosis.[26]

Conclusion

Several new ACTs are under development,[28] co-formulated amodiaquine-artesunate has recently been prequalified by WHO, dihydroartemisinin-piperaquine is already being used in southeast Asia and many parts of Africa, and has proved to be very efficacious.[29–31] Dihydroartemisinin-piperaquine manufactured according to internationally recognised good manufacturing practices is likely to be available soon, and other new drugs, including those that are modifications of existing antimalarial drugs and those with a novel mode of action, are entering clinical trials. Therefore, there are good prospects for effective new treatments to be used as second-line treatment instead of quinine.

A major obstacle to large-scale use of ACTs as first-line and second-line drugs is their cost and availability in the public and private sector. However, several initiatives that aim to increase access could overcome these barriers, including the use of community health workers and the improvement of the public-sector procurement and supply-chain system to limit stock outs. Furthermore, reduction in the cost of ACTs, particularly in the private sector through subsidy schemes or through the Affordable Medicines for Malaria facility, has recently been approved by the Global Fund for HIV, Tuberculosis, and Malaria board to enter phase I, and could make ACTs much more affordable for the rural poor. Finally, ongoing research and development for synthetic artemisinins make us more confident that oral quinine monotherapy will soon be a drug of the past.

Conflicts of interest

We declare that we have no conflicts of interest. AT and UD'A have been invited to speak at scientific symposia organised by Novartis Pharma and Sanofi Aventis. UD'A has received a research grant from Sigma Tau.

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