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Current clinical efficacy of chloroquine for the treatment of Plasmodium falciparum infections in urban Dar es Salaam, United Republic of Tanzania

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Current clinical efficacy of chloroquine for the treatment of *Plasmodium falciparum* infections in urban Dar es Salaam, United Republic of Tanzania

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Reported is the use of a 14-day WHO protocol, which takes into account the clinical, parasitological and haematological responses to antimalarial drugs, to determine the efficacy of chloroquine in the treatment of uncomplicated malaria in young children ($n = 200$) in urban Dar es Salaam. Chloroquine failure was found in 43% of the children. Of these, 12.5% were considered to be early treatment failures and were given a single dose of sulfadoxine–pyrimethamine. Fever subsided in all children treated with sulfadoxine–pyrimethamine and there were no parasitological failures. In addition, children treated with sulfadoxine–pyrimethamine because of early treatment failure with chloroquine had better haematological recovery than the chloroquine-sensitive group. It is concluded that chloroquine can no longer be considered an effective therapy for *P. falciparum* malaria in young children in Dar es Salaam.

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Introduction

Since the emergence of chloroquine-resistant falciparum malaria in the United Republic of Tanzania (*1*) there has been an upward trend in the frequency and degree of the resistance (*2*). Nevertheless, chloroquine remains the official first-line antimalarial drug in the United Republic of Tanzania, while neighbouring Malawi and Kenya have already replaced chloroquine with sulfadoxine–pyrimethamine as first-line treatment for nonsevere malaria in young children (*3*).

Antimalarial drug resistance has previously been assessed mainly by determining parasite clearance in asymptomatic children (*4*). However, resistance rates based on parasite clearance only are inadequate for making decisions about drug efficacy: evidence of a lack of clinical response is also needed. A 14-day protocol which takes into account both symptomatic resolution and parasite clearance has therefore recently been proposed by WHO (*5*).

This study reports our experience with the protocol and the status of *Plasmodium falciparum* sensitivity to chloroquine in Dar es Salaam.

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Materials and methods

Study site

The study was carried out at Temeke district hospital during the peak malaria transmission season in 1997 (May–August). The hospital serves a population of about 800 000 people in Temeke district, one of the three administrative districts within the city of Dar es Salaam.

Study procedure

The WHO protocol for assessing the therapeutic efficacy of antimalarial drugs against uncomplicated falciparum malaria in areas with intense transmission (*5*) was followed. Children aged 6–60 months who were attending the outpatient department of the hospital were recruited. Inclusion criteria were as specified in the protocol with the exception that children with a history of fever in the preceding 12 hours but without raised axillary temperature at attendance were also enrolled.

Children were examined clinically to exclude other causes of fever, their axillary temperatures and weights were measured, blood slides to evaluate parasitaemia were prepared, and packed cell volumes were also determined. Those children meeting the parasite density criteria (2000 asexual parasites per μl) were enrolled and oral chloroquine treatment was administered under supervision.

Follow-up

All children recruited were seen at the hospital again on day 1 and day 2 for clinical examination and chloroquine administration. Subsequently they were seen on day 3 and day 7 for preparation of blood slides, and those who were treatment failures were

given a single dose of sulfadoxine–pyrimethamine. The children were again seen on day 14, when in addition to the clinical examination and blood slide preparation a repeat determination of packed cell volume was carried out.

Drug treatment

All children were treated with chloroquine tablets (150 mg of chloroquine phosphate, Helm Pharmaceuticals GmbH, Hamburg, Germany) at a dosage of 25 mg/kg body weight, given as 10 mg/kg body weight on days 0 and 1 and 5 mg/kg body weight on day 2. In all cases of chloroquine treatment failure, sulfadoxine–pyrimethamine (Fansidar®, Hoffmann-La Roche, Basel, Switzerland) (1.25mg pyrimethamine/kg body weight) was given. In addition, for ethical reasons, paracetamol tablets were also given for the first 2 days and during the follow-up if fever was documented.

Laboratory examination

Thick and thin blood smears were made on the same slide and stained with 5% Giemsa at pH 7.2 for 20 min. Parasite density was assessed by counting the number of asexual parasites per 200 leukocytes in the thick smear. Parasite numbers were converted to a count per μl by assuming a standard leukocyte count of 8000 per μl. Species were confirmed by examining the thin film. Blood for packed cell volume determination was centrifuged using the standard haematocrit centrifuge (UL Adams Autocrit Centrifuge, USA) and the percentage of packed red cells in the plasma was recorded.

Classification of therapeutic responses

Three categories of therapeutic responses were defined.

- Early treatment failure. If the patient developed one of the following during the first three days of follow-up:
  - danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitaemia;
  - axillary temperature of $\geqslant$ 37.5 °C on day 2 with parasitaemia greater than that on day 0;
  - axillary temperature of $\geqslant$ 37.5 °C on day 3 in the presence of parasitaemia;
  - parasitaemia on day 3 $\geqslant$ 25% of the count of day 0.
- Late treatment failure. If the patient developed one of the following during the follow-up period from day 4 to day 14:
  - danger signs or severe malaria in the presence of parasitaemia on any day from day 4 to day 14, if none of the criteria of early treatment failure have previously been met;
  - axillary temperature $\geqslant$ 37.5 °C in the presence of parasitaemia from day 4 to day 14, if none of the criteria of early treatment failure have previously been met.
- Adequate clinical response. If the patient showed one of the following during the follow-up period, i.e. up to 14 days.
  - absence of parasitaemia on day 14 irrespective of axillary temperature, if none of the criteria of early or late treatment failure have previously been met;
  - axillary temperature < 37.5 °C irrespective of the presence of parasitaemia, if none of the criteria for early or late treatment failure have previously been met.

Results

A total of 608 children were screened in the outpatient department and, of these, 486 (80%) had parasitaemia. However, only 259 children (53%) fulfilled the criteria for enrolment. One child developed symptoms of severe malaria after the first dose of chloroquine and was therefore excluded from the study. During the follow-up, 58 children dropped out. A complete set of data was thus available for 200 children. Baseline clinical and laboratory characteristics are shown in Table 1.

Table 1. **Baseline characteristics of the study patients (*n* = 200)**

Mean age ± SD (months)	28.2 ± 16.5
Weight ± SD (kg)	11.0 ± 3.2; (6–20)[a]
No. of reported antimalarial treatments in preceding week	30; *15*[b]
No. with a history of fever in preceding 12 hours	199; *99.5*
No. with axillary temperature $\geqslant$ 37.5 °C	154; *77*
Geometric mean parasitaemia density (per μl)	6 404 (2 000–152 000)
Mean packed cell volume ± SD	27.5% ± 5.1

[a] Figures in parentheses are the range.

[b] Figures in italics are percentages.

Clinical response to chloroquine

A total of 114 (57%) children had adequate clinical response as well as parasite clearance by day 14 and had therefore been successfully treated with chloroquine. The remaining 86 (43%) children exhibited chloroquine treatment failure. Early treatment failure was recorded in 25 children (12.5% (95% confidence interval (CI), 7.9–17.1)) and late treatment failure was recorded in 61 children (30.5% (95% CI, 24.1–36.9)). Of the 61 children with late treatment failure, 28 (45.9%) had been registered as such by day 7, while the remaining 33 (54.1%) were registered on day 14. Table 2 shows the fever and parasitaemia profiles of the children with treatment failure.

Initial parasitaemia and therapeutic response

The outcome of patients with low parasitaemia (<5000 asexual parasites per μl) at recruitment was compared with those whose recruitment parasitae-

Table 2. **Temperature and parasitaemia profiles of children after chloroquine treatment failure (*n* = 86)**

	Day 3 (*n* = 25)	Day 7 (*n* = 28)	Day 14 (*n* = 33)
No. with temperature ⩾37.5 °C	17; *68*[a]	20; *71*	23; *70*
Geometric mean parasitaemia density (per μl)	7 (50–84 000)[b]	5 829 (1 680–40 000)	5 807 (1 200–51 600)
Mean packed cell volume	27.1%[c]; 29.5%[d]	28.6%[c]; 28.1%[d]	28.6%[c]; 27.3%[d]

[a] Figures in italics are percentages.

[b] Figures in parentheses are the range.

[c] Packed cell volume at enrolment.

[d] Repeat packed cell volume on day 14 (all treatment failures with chloroquine were given sulfadoxine–pyrimethamine).

mia was ⩾5000 asexual parasites per μl. The failure rate was 37.2% for children whose parasite count was low, while for those whose parasite count was high the failure rate was 50.6%. The difference in failure rates between those with low and high parasitaemias at recruitment was not significant. The rate ratio was 1.27 (95% CI, 0.98–1.64)

Clinical response to sulfadoxine–pyrimethamine

Parasitaemia cleared in all children treated with sulfadoxine–pyrimethamine after treatment failure with chloroquine. There was no reported history of fever a day after treatment and no child subsequently had raised axillary temperature.

Haematological response

The mean packed cell volume at enrolment of children with early treatment failure was 27.1%. These children were treated with sulfadoxine–pyrimethamine and at day 14 the repeat packed cell volume was 29.5% (a rise of 2.4%). The mean packed cell volume of children with adequate clinical response (success) at enrolment was 27.1% and their repeat mean packed cell volume on day 14 was 27.2%. The mean changes in packed cell volume of early treatment failures and adequate clinical response groups were compared and the difference was found to be statistically significant (Student's *t* test 9.8, $P < 0.001$). The early treatment failure group showed a significant improvement in their anaemic status after treatment with sulfadoxine–pyrimethamine (Table 2).

The anaemic status of children with late treatment failure (day 7 and 14) did not improve despite treatment with sulfadoxine–pyrimethamine. This could have arisen because we were not able to follow up the late treatment failure cases for long enough after sulfadoxine–pyrimethamine treatment to assess their haematological response.

Discussion

There are many anecdotal and published reports of decreased chloroquine efficacy from some areas of the United Republic of Tanzania. Countrywide chloroquine sensitivity studies conducted by the National Institute of Medical Research have demonstrated varying degrees of resistance *in vivo* and *in vitro* in the regions tested so far. The median *in vivo* resistance rate in asymptomatic schoolchildren was 20% (*6*). However, the exact levels of chloroquine efficacy, especially in urban areas where drug pressure may be higher, remain unknown. This study shows a treatment failure rate greater than 40%. Reports from elsewhere in the United Republic of Tanzania indicate a failure rate of 40–50% (*7*).

There are as yet no generally accepted guidelines for policy-makers considering a change in first-line therapy for malaria. However, Schapira et al. (*8*) affirm that, on the basis of maintaining effective treatment at reasonable cost, a drug with a failure rate of more than 25–35% should not be used as first-line treatment for young children if a more suitable alternative is available. Sudre et al. (*9*) argue that when the prevalence of RIII resistance in young children is greater than 14–31%, depending on compliance, sulfadoxine–pyrimethamine is the most cost-effective treatment despite its 45% higher price. Bloland et al. (*3*) propose that when 5–10% of cases are RIII resistant, the duration of clinical improvement and haematological recovery should be considered. Our results suggest that haematological recovery is better in children treated with sulfadoxine–pyrimethamine. This is an important observation since malarial anaemia is a major cause of morbidity and mortality in malaria-endemic areas (*10*). The high treatment failure rate seen with chloroquine and its low impact on the anaemic status of children call for a change in the official drug policy. Clearly, chloroquine is no longer effective at decreasing malaria morbidity among under-5-year-olds in the study area.

Sulfadoxine–pyrimethamine will be the probable replacement for chloroquine in the United Republic of Tanzania. However, there are already reports of alarming levels of sulfadoxine–pyrimethamine resistance in areas where it has routinely been used (*11*). As a result, there will be a greater need for close routine monitoring of antimalarial efficacy. We believe that a 3-day follow-up to detect early treatment failures can be incorporated into the existing health system at the district level in the United Republic of Tanzania. However, such a follow-up period cannot provide data on haematological response, and therefore an early treatment failure rate of 5–10% may warrant a 14-day follow-up by research teams to confirm the extent of the problem and make recommendations as appropriate.

Applicability of the WHO protocol

Our experience with the study protocol is positive and the protocol is suitable for use in malaria-endemic areas. The diagnosis of an acute malarial

episode remains a controversial issue in community surveys, especially whether to include children with a reported history of fever in the absence of raised axillary temperature. A history of fever reported by the mother during the preceding 12 hours correlated well with a malaria episode in this study, and we suggest that it be incorporated in the inclusion criteria.

Some statistical evidence suggested that the treatment outcome depended on the level of baseline parasitaemia. We suggest that the inclusion criterion for parasite density be raised from 2000 to 5000 per μl. A combination of a history of fever in the preceding 12 hours and a higher parasite density in the inclusion criteria will guard against decreased specificity resulting from children with a history of fever only. In endemic areas during the peak transmission season the criteria of a history of fever and higher parasitaemia will permit recruitment of more children. This will not have an impact on the outcome of the study and will enable surveys to be carried out more rapidly and with reduced costs.

Conclusions

We conclude from these results that there is a relatively high rate of chloroquine treatment failure in Dar es Salaam. It is not clear, however, how widespread this problem is throughout the country and a rapid assessment of this should be carried out on a national scale using the approach described here. Should the efficacy of chloroquine throughout the United Republic of Tanzania prove to be as poor as it is in Dar es Salaam, the ethics and rationale of continuing to maintain chloroquine as the first-line drug for the treatment of malaria must seriously be questioned.

Our observations suggest that sulfadoxine–pyrimethamine may be considered as a replacement for chloroquine to treat uncomplicated malaria in Dar es Salaam, but nationwide data on its current efficacy in the United Republic of Tanzania are urgently needed. In addition, a practical surveillance system will need to be established, so that the alarm can be raised in sufficient time when treatment failure occurs in the future. The recent initiative, The East African Network for Monitoring Antimalarial Treatment, is a step in the right direction in this respect.

The WHO protocol for assessment of therapeutic efficacy was found to be practical in our hands but the inclusion criteria may require modification. ■

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Résumé

Efficacité clinique actuelle de la chloroquine dans le traitement du paludisme à *Plasmodium falciparum* à Dar-es-Salaam (République-Unie de Tanzanie)

Nous avons utilisé un protocole thérapeutique de l'OMS relativement nouveau qui prend en compte la réponse clinique, parasitologique et hématologique aux antipaludéens pour évaluer l'efficacité thérapeutique de la chloroquine dans le traitement du paludisme sans complications chez des enfants en bas âge (n = 200) dans la zone urbaine de la ville de Dar-es-Salaam (République-Unie de Tanzanie). On a constaté un échec du traitement chez 43% des enfants, et parmi eux, 12,5% ont été considérés comme des échecs thérapeutiques précoces et ont reçu une dose unique de sulfadoxine-pyriméthamine. La fièvre est tombée chez tous les enfants traités par cette association et il n'y a pas eu d'échec thérapeutique au sens parasitologique. En outre, les enfants traités par la sulfadoxine-pyriméthamine ont mieux récupéré sur le plan hématologique que ceux du groupe dont l'infection avait cédé à la chloroquine.

La conclusion que nous tirons de ces résultats, c'est que les infections palustres qui ne cèdent pas à la chloroquine sont relativement fréquentes à Dar-es-Salaam. On ne sait pas exactement, cependant, dans quelle mesure le même problème se pose sur l'ensemble du territoire tanzanien et il serait donc indiqué de procéder à une enquête rapide à l'échelle nationale. Si cette enquête montre que le traitement par la chloroquine donne dans l'ensemble du pays des résultats aussi médiocres qu'à Dar-es-Salaam, il faudra se poser la question de savoir s'il est raisonnable et moralement justifié de continuer à considérer la chloroquine comme l'antipaludéen de première intention en République-Unie de Tanzanie.

Nos observations donnent à penser qu'on pourrait envisager de remplacer la chloroquine par l'association sulfadoxine-pyriméthamine pour traiter les cas de paludisme sans complications à Dar-es-Salaam. Toutefois, il est urgent d'obtenir davantage de données sur son efficacité actuelle dans l'ensemble du territoire. En outre, il faudra mettre en place un système pratique de surveillance de manière qu'à l'avenir, on puisse traiter, en temps utile, les cas d'échec thérapeutique. Dans cette optique, l'initiative, qui a été récemment prise en Afrique, de créer un réseau baptisé East African Network for Monitoring Antimalarial Treament, va dans le bon sens.

Resumen

Eficacia clínica actual de la cloroquina en el tratamiento de las infecciones por *Plasmodium falciparum* en las zonas urbanas de Dar-es-Salaam, República Unida de Tanzanía

Utilizamos el nuevo protocolo de la OMS en el que se tienen en cuenta las respuestas clínica, parasitológica y hematológica a los medicamentos antipalúdicos para determinar la eficacia de la cloroquina en el tratamiento del paludismo no complicado en niños de corta edad (n = 200) en las zonas urbanas de Dar-es-Salaam, República Unida de Tanzanía. La cloroquina no surtió efecto en un 43% de los niños; en el 12,5% de los casos fracasó el tratamiento inicial y se administró una dosis única de sulfadoxina-pirimetamina (S-P). La fiebre remitió en todos los niños tratados con S-P, al igual que la parasitemia. Además, los niños tratados con S-P de esta manera presentaron una mejor recuperación hematológica que el grupo sensible a la cloroquina.

Concluimos a partir de estos resultados que en la población de Dar-es-Salaam hay un nivel relativamente alto de resistencia a la cloroquina. Sin embargo no está claro si se trata de un problema generalizado en el país, por lo que convendría realizar una evaluación rápida a escala nacional. Si la eficacia terapéutica de la cloroquina en todo el país resulta ser tan baja como en Dar-es-Salaam, habrá que replantearse la ética y la lógica del mantenimiento de la cloroquina como medicamento antipalúdico de primera línea en Tanzanía.

Nuestras observaciones indican que la combinación sulfadoxina-pirimetamina puede considerarse una alternativa a la cloroquina en el tratamiento del paludismo no complicado; sin embargo, se necesitan urgentemente más datos a escala nacional sobre su actual eficacia. Además, habrá que poner en marcha un sistema práctico de vigilancia, para que en el futuro se pueda alertar prontamente de los casos de fracaso terapéutico. En este sentido, la Red de África Oriental para la Vigilancia de los Tratamientos Antipalúdicos, iniciativa lanzada recientemente, es un paso en la dirección correcta.

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