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Evaluation of four therapeutic regimens for falciparum malaria in Mozambique, 1986

A. SCHAPIRA[1] & J. F. L. SCHWALBACH[2]

A randomized study on the effect of the following four treatment regimens on Plasmodium falciparum *parasitaemia was carried out on 200 asymptomatic schoolchildren in Maputo, Mozambique: chloroquine (25 mg/kg body weight), amodiaquine (25 mg/kg), sulfadoxine–pyrimethamine (25 mg/kg and 1.25 mg/kg), or amodiaquine (25 mg/kg) + sulfadoxine–pyrimethamine (25 mg/kg and 1.25 mg/kg) administered on the third day of the study. The results of* in vivo *tests indicated that 94% of the infections were resistant to chloroquine, 76% to amodiaquine, and 16% to sulfadoxine–pyrimethamine. The cure rate with amodiaquine + sulfadoxine–pyrimethamine was 100%, which was not significantly different from that with sulfadoxine–pyrimethamine alone; the latter regimen was the most rapidly acting of the treatments studied. It is concluded that amodiaquine is not an appropriate substitute for chloroquine, but that the effect of the combination amodiaquine + sulfadoxine–pyrimethamine may be superior to that of sulfadoxine–pyrimethamine alone, although this requires further study.*

The spread of chloroquine-resistant malaria in Africa makes it necessary to define alternative treatment regimens for cases that display such resistance or for use in areas where chloroquine has lost its therapeutic value. Sulfadoxine–pyrimethamine is the traditional substitute for chloroquine, but resistance to this combination has developed with deplorable speed in south-east Asia (*1*) and has been reported also in East Africa (*2*). Amodiaquine has been shown to retain some efficacy in Kenya (*3*), despite the presence of chloroquine resistance in the country, and has been recommended by some groups for first-line treatment in cases of chloroquine failure (*4*).

The present study was undertaken to investigate whether the combination of amodiaquine and sulfadoxine–pyrimethamine might remain effective despite the possible presence of resistance to the separate components. The effect of four treatment regimens—chloroquine, amodiaquine, sulfadoxine–pyrimethamine, and amodiaquine + sulfadoxine–pyrimethamine—was investigated in a randomized trial using an *in vivo* test methodology supplemented by *in vitro* drug susceptibility assays.

MATERIALS AND METHODS

Study area

The study was carried out from May to September 1986 in Machava district, Maputo, Mozambique, a semi-urban area with perennial transmission of malaria that is exacerbated from February to May. In 1985,[a] 78% of *Plasmodium falciparum* isolates in Maputo were chloroquine resistant *in vitro*. The only control measure available against malaria in the area is presumptive treatment with chloroquine through primary health care.

Subjects

Schoolchildren from three primary schools were screened from May to September 1986 by examination of samples of capillary blood. Those who exhibited more than 800 asexual *P. falciparum parasites* per μl upon on-the-spot microscopic study of 10 fields were selected. Each carrier was then carefully questioned about whether they had taken chloroquine over the previous 14 days, and, if this was denied, the child was entered in the study. When

[1] Research Fellow, Malaria Department, Instituto Nacional de Saúde, Maputo, Mozambique.

[2] Chief, Malaria Department, and Director, Instituto Nacional de Saúde, C.P. 264, Maputo, Mozambique. Requests for reprints should be sent to this author.

[a] INSTITUTO NACIONAL DE SAÚDE. [*The susceptibility of* P. falciparum *to chloroquine in Maputo*]. Maputo, Instituto Nacional de Saúde, 1985 (in Portuguese).

possible, the information given by a child was checked by questioning a parent. The Dill-Glazko test for the presence of aminoquinolines in the urine was not used, because we have previously found it to be unreliable (*5*).

Most of the parasite carriers were asymptomatic, but some had fever and headache. Severely ill children did not participate in the study, but were given routine treatment and followed up. Before the start of the investigation, parents were informed of the trial and its objectives and those who did not wish their child to participate were asked to advise the headmaster. Children were removed from the study if they did not complete their treatment or if they were lost from follow-up before day 14 of the trial. A total of 200 children took part in the study.

Treatment

Randomization was performed reiteratively in order to create four groups of 50 children who were assigned to one of the following treatments, which were written on cards kept in envelopes numbered from 1 to 200 and opened as the children entered the trial:

—chloroquine diphosphate,[b] 25–30 mg base per kg body weight over 3 days (10+10+5 mg/kg);
—amodiaquine hydrochloride,[c] same dosage as chloroquine diphosphate;
—sulfadoxine–pyrimethamine,[d] 25–30 mg sulfadoxine and 1.25–1.5 mg pyrimethamine per kg as a single dose; and
—amodiaquine (25–30 mg base per kg over 3 days (10+10+5 mg/kg)) supplemented on the third day of the trial (day 2) with sulfadoxine–pyrimethamine (25–30 mg sulfadoxine and 1.25–1.5 mg pyrimethamine per kg) together with 5 mg/kg amodiaquine.

In the last-mentioned treatment regimen, sulfadoxine–pyrimethamine was given only on the third day, because it was assumed *a priori* that amodiaquine acted more rapidly than sulfadoxine–pyrimethamine; also, especially in symptomatic patients, it was feared that giving both amodiaquine and sulfadoxine–pyrimethamine at the start of the treatment might cause vomiting.

No placebo was given. Treatment was given under the authors' direct supervision, and the children were kept under observation for 30 minutes after each dose.

The quality of the amodiaquine tablets was controlled by the Ministry of Health's Laboratory for Control of Quality of Drugs (B.P. 82, Mr J. Neves de Figueiredo).

The WHO 28-day test (*6*) was carried out with the following modifications: thick films of blood were prepared daily from day 0 to day 9 (except Sundays) and on days 14, 21, 28, and 35. For all films 100 microscope fields were examined and the asexual and sexual plasmodia present counted against 500 leukocytes, or, if very rare, in 100 fields, corresponding to approximately 2000 leukocytes. The results of the *in vivo* tests were classified using standard WHO criteria (*6*) and only cases that had been followed for 28–35 days or those proven to be resistant earlier were included. Recrudescences in RI cases were classified as early, if present before or on day 14, otherwise as late. The study was not blind, but the microscopists were not aware of the treatment regimen that had been assigned to individual children.

In vitro *tests*

Before the start of treatment, 200 μl of capillary blood was drawn into heparinized capillary tubes and transferred immediately to 1.8 ml of RPMI 1640 medium[e] containing 25 mmol/l HEPES buffer, 25 mmol/l sodium bicarbonate, and 40 mg/l gentamicin. This suspension was used for standard WHO "micro" *in vitro* schizont maturation tests[f] with chloroquine (plate batches C-66, C-79, C-80, C-83, and C-84), amodiaquine (plate batches 11 February 1985, A-3 and A-9). The results with amodiaquine plates A-3 and A-9 were later found to be invalid and are not reported. The residual blood and medium suspension was used to carry out a merozoite reinvasion test for pyrimethamine susceptibility (*7*). After centrifugation for 5 minutes at 114 *g*, the supernatant was carefully withdrawn with an Eppendorf pipette, replaced with RPMI 1640 medium supplemented with 10% non-immune-type AB serum, and the erythrocyte volume fraction adjusted to 2%. Aliquots of 100 μl were placed in the wells of microtitration plates that were pre-dosed with pyrimethamine[g] to yield final concentrations of the drug of 0, 0.03, 0.1, 0.3, 1, 3, 10, and 30 μmol/l. The tests were harvested after 48 hours' incubation at 37–38 °C, thin films being made from the cells in each well. These were examined by counting the number of young rings in either 4000 erythrocytes per film or in 100 fields corresponding to 10 000—15 000 erythrocytes, if only a few rings were visible in the

[b] Avloclor, ICI, lot PA 51/7/1.
[c] Pharmachemic, batch 83 J 09/1.
[d] Fansidar, Hoffmann-La Roche, lot B 4093 MFD 0583.
[e] Gibco, Paisley, Scotland.
[f] PAYNE, D. *Practical aspects of the use of the standard WHO* in vitro *macro- and microtest systems for the determination of the sensitivity of* Plasmodium falciparum *to chloroquine, mefloquine, amodiaquine, and quinine*. Unpublished WHO document MAP/84.2, 1984.
[g] Wellcome, Research Triangle Park, NC, USA.

Table 1. Some characteristics of the children in the four treatment groups

	Chloroquine	Amodiaquine	Sulfadoxine–pyrimethamine	Amodiaquine + sulfadoxine–pyrimethamine
No. of children	33	35	35	28
Mean age (years)	9.7 (2.5)[a]	9.8 (2.2)	10.6 (2.2)	9.9 (2.2)
Geometric mean parasitaemia level on day 0 (asexual *P.f.* /μl)	6150 (1.72)	5330 (3.87)	5480 (3.88)	3980 (3.88)
Mean dose (mg/kg body weight)	26.2 (1.8)	25.9 (0.90)	29.0 (3.7)[c] + 1.45 (0.19)[d]	26.0 (1.0)[b] + 26.7 (2.8)[c] + 1.34 (0.14)[d]

[a] Figures in parentheses are standard deviations.
[b] Values are for amodiaquine.
[c] Values are for sulfadoxine.
[d] Values are for pyrimethamine.

control. A test was rejected if 10 young rings could not be found in the control.

For both types of *in vitro* tests, minimal inhibitory concentrations (MIC) were defined as the lowest concentration that caused complete inhibition of schizont maturation or merozoite re-invasion. The concentrations that resulted in 50% inhibition of parasite development (IC_{50}) were calculated by regression analysis.[h]

[h] GRAB, B. & WERNSDORFER, W. H. *Evaluation of* in vitro *tests for drug sensitivity in* Plasmodium falciparum: *probit analysis of log dose/response test from 3–8 points assay.* Unpublished document WHO/MAL/83.990, 1983.

RESULTS

In vivo *tests*

During the survey, the *P. falciparum* infection rate in the screened children declined from 37.1% in May to 14.2% in September 1986.

Some characteristics of the children in the four treatment groups are shown in Table 1. There were no significant differences between the groups as far as age, initial parasitaemia level, and dosage of amodiaquine or of sulfadoxine–pyrimethamine were concerned (single classification ANOVA, $P > 0.05$). Of

Table 2. Results of the 28-day *in vivo* test with four treatments for *Plasmodium falciparum* malaria in Maputo, Mozambique, 1986[a]

	Chloroquine		Amodiaquine		Sulfadoxine–pyrimethamine		Amodiaquine + sulfadoxine–pyrimethamine	
	n	%	*n*	%	*n*	%	*n*	%
S	2	6.1	8	24.2	21	84.0	22	100
RI, late recrudescence	7	21.2	17	51.5	3	12.0	0	0
RI, early recrudescence	20	60.6	8	24.3	0	0	0	0
RII	3	9.1	0	0	1	4.0	0	0
RIII	1	3.0	0	0	0	0	0	0
Total	33		33		25		22	
Mean parasite clearance time (days)	2.48 (0.21)[b]		2.23 (0.59)		1.85 (0.33)		2.04 (0.68)	

[a] Cases were followed for 28–35 days or diagnosed as resistant before this time.
[b] Figures in parentheses are standard deviations.

the 200 children who entered the study, 69 were later excluded, because the initial parasitaemia, when rechecked, was too low, because of non-compliance with treatment or because they were lost from follow-up before day 14. Non-compliance was less frequent for the sulfadoxine–pyrimethamine group than for the others.

The results of the *in vivo* test shown in Table 2 clearly separate the treatments into two groups: those including sulfadoxine–pyrimethamine, with an overall cure rate of 91%, and those including only a 4-aminoquinoline, with an overall cure rate of 15%. Within these groups, there is a significant difference between the outcomes of the amodiaquine and chloroquine treatments (Mann-Whitney test, $P<0.05$), but not between those of sulfadoxine–pyrimethamine with and without amodiaquine ($P=0.18$). Mean parasite clearance times were significantly lower for monotherapy with sulfadoxine–pyrimethamine than with chloroquine or amodiaquine (Student's t-test, $P<0.05$), but the difference between the two sulfadoxine–pyrimethamine regimens was not significant. Fig. 1, which shows the mean parasite densities as a proportion of their initial values, indicates that the most rapid clearance was obtained with sulfadoxine–pyrimethamine. Also, it should be noted that the therapy with amodiaquine differs from that with chloroquine mainly in terms of late recrudescences.

The frequency of gametocyte patency in the four groups is shown in Fig. 2. All the treatment regimens were associated with an increase in the gametocyte index, which reached a maximum on day 7–8 and

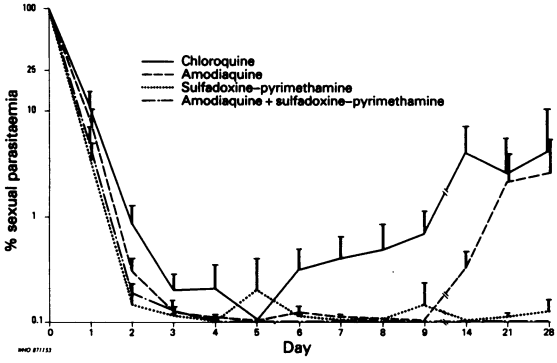

Fig. 1. Geometric mean and standard error of the mean for density of asexual *Plasmodium falciparum* parasites expressed as a proportion of that on day zero + 0.1 during and after treatment with chloroquine, amodiaquine, sulfadoxine–pyrimethamine, or amodiaquine + sulfadoxine–pyrimethamine.

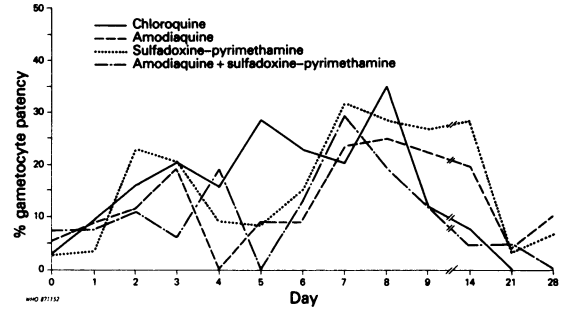

Fig. 2. Frequency of *Plasmodium falciparum* gametocyte patency during and after treatment with chloroquine, amodiaquine, sulfadoxine–pyrimethamine, or amodiaquine + sulfadoxine–pyrimethamine.

declined towards day 21–28. Gametocytaemia was less prolonged for those treated with amodiaquine + sulfadoxine–pyrimethamine than for those who received sulfadoxine–pyrimethamine, but the difference between the number of person–days with gametocytaemia in the two groups was not significant (χ^2 test, $P>0.05$). With the exception of one patient who was treated with chloroquine and became positive on day 35 of the study, the results of the *in vivo* tests on day 35 did not alter the *in vitro* test classifications obtained on day 28.

In vitro *tests*

The distributions of the MIC and IC_{50} values for chloroquine and amodiaquine are shown in Table 3. There is no clear correlation between the *in vivo* and *in vitro* test results. According to criteria used by WHO, the MIC values for chloroquine in the *in vitro* tests indicate that 92.8% of cases were resistant to the drug, which is almost identical to the level of resistance determined from the results of the *in vivo* tests (Table 2). For amodiaquine, where an MIC $\geqslant 4$ μmol/l is considered to be indicative of resistance (W. H. Wernsdorfer, personal communication, 1985), the frequency of resistance *in vitro* was 35.3%, which differs significantly from that *in vivo* of 75.8% (χ^2 test, $P<0.05$).

The IC_{50} and MIC values for pyrimethamine are compared with the *in vivo* results in Table 4. The one case that was resistant to sulfadoxine–pyrimethamine, and which had a successful *in vitro* test, had an IC_{50} value $\geqslant 3$ μmol/l, which previous studies have shown to be associated with *in vivo* resistance to this combination (*2*). A similar *in vitro* result was found in a case which was cured by amodiaquine + sulfadoxine–pyrimethamine. The frequency of isolates with IC_{50}

Table 3. Correlation of the results of the *in vitro* tests for chloroquine and amodiaquine and *in vivo* tests for all treatments

	In vivo test response								
	Chloroquine			Amodiaquine		Sulfadoxine–pyrimethamine		Amodiaquine + sulfadoxine–pyrimethamine	
In vitro test result	S	RI	RII	S	RI	S	RI	S	Total[a]
Chloroquine[b]									
n	2	12	2	2	13	8	1	6	69
MIC ⩾1.6 μmol/l	1	11	1	2	12	8	1	6	64 (92.8%)
MIC ⩽1.14 μmol/l	1	1	1	—	1	—	—	—	5 (7.2%)
Mean IC_{50} (μmol/l)	0.66 (0.27)[c]	1.52 (0.26)	0.44 (0.17)	1.79 (0.10)	1.51 (0.30)	0.91 (0.31)	0.68	1.50 (0.19)	1.38 (0.11)
Amodiaquine[d]									
n	2	3	—	—	5	1	—	4	17
MIC ⩾0.4 μmol/l	1	—	—	—	3	—	—	1	6 (35.3%)
MIC ⩽0.2 μmol/l	1	3	—	—	2	1	—	3	11 (64.7%)
Mean IC_{50} (μmol/l)	0.21	0.10 (0.01)	—	—	0.08 (0.01)	—	—	0.18 (0.09)	0.12 (0.02)

[a] The total number of *in vitro* tests conducted was greater than the sum of the numbers in the groups, because some were not complemented by *in vivo* tests.
[b] A minimal inhibitory concentration (MIC) ⩾1.6 μmol/l was taken to be indicative of drug resistance.
[c] Figures in parentheses are the standard error of the mean.
[d] A minimal inhibitory concentration (MIC) ⩾0.4 μmol/l was taken to be indicative of drug resistance.

values ⩾3 μmol/l was 6.3%, which is not significantly different from that of the *in vivo* resistance to sulfadoxine–pyrimethamine. Of the MIC values, 31.7% were ⩾3 μmol/l, which suggests the presence of a low proportion of highly resistant parasites in a high proportion of the infections.

There is a marginal correlation between the degree of *in vivo* susceptibility to chloroquine and the pyrimethamine IC_{50} value (Spearman's $\varrho = 0.87$; $0.1 > P > 0.05$), but not between amodiaquine *in vivo* susceptibility and the pyrimethamine IC_{50} value ($\varrho = 0.16$; $P > 0.1$).

Table 4. Correlation of the *in vitro* tests with pyrimethamine and *in vivo* test results for all treatments

	In vivo test response[a]															
	Chloroquine				Amodiaquine				Sulfadoxine–pyrimethamine				Amodiaquine + Sulfadoxine–pyrimethamine			
Concentration of pyrimethamine *in vitro* (μmol/l)	S/RI		RII		S		RI		S		RI		S		Total[b]	
	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC
⩾30	—	1	—	—	—	—	—	—	—	3	—	1	—	1	—	8
3–29.9	—	1	—	2	—	1	1	2	—	1	1	—	1	2	4	12
0.3–2.99	1	—	1	—	—	—	1	1	—	—	—	—	—	5	5	12
0.03–0.29	1	4	1	—	1	1	—	3	3	4	—	—	3	6	11	31
<0.03	4	—	—	—	1	—	4	—	5	—	—	—	10	—	43	—
Total	6		2		2		6		8		1		14		63	

[a] An IC_{50} ⩾3 μmol/l was considered to be indicative of resistance.
[b] The total number of *in vitro* tests carried out was greater than the sum of the numbers in the groups, because some were not complemented by *in vivo* tests.

DISCUSSION

Both *in vivo* and *in vitro* results indicate a high frequency of chloroquine resistance in *P. falciparum* infections in the study area, and the level of *in vitro* resistance is probably associated with a higher degree of *in vivo* resistance among non-immunes.

With amodiaquine, the *in vivo* results were only marginally better than with chloroquine, a finding that is consistent also with the outcome of a 28-day *in vivo* study of amodiaquine in Rwanda (*8*). Interestingly, had *in vivo* tests been performed only as far as day 7 or 14 of the study, amodiaquine would have appeared markedly superior to chloroquine. Late recrudescence is indistinguishable from reinfection, but, even with very high inoculation rates, reinfection could only account for a small proportion of the 51.5% of cases treated with amodiaquine that were classified as RI late recrudescence (*9*). Also, the declining parasite rate during the study implies that the inoculation rate was low.

The difference between *in vivo* and *in vitro* results with amodiaquine may possibly have arisen because of reinfection; however, amodiaquine is a pro-drug, whose active metabolite, monodesethylamodiaquine, is less active than the parent compound (*10*). It still seems uncertain whether *in vitro* tests with amodiaquine are an adequate epidemiological tool.

The high degree of susceptibility to pyrimethamine and the corresponding high cure rate and rapid effect of sulfadoxine–pyrimethamine is encouraging, but the *in vitro* results suggest that there is the potential for rapid evolution of sulfadoxine–pyrimethamine resistance in the study area. Our findings indicate that there was a combination of a high degree and frequency of resistance to 4-aminoquinolines and a high degree of antifolate susceptibility in the study area. This contrasts with results from south-east Asia (*1*) and with those from a study of highly selected East African material (*11*), but resembles the findings in Kenya reported in 1983 (*12*). Antifolate resistance in chloroquine-resistant areas is therefore probably mainly conditioned by specific drug pressure.

The results of the *in vivo* tests do not conclusively establish whether the combination of sulfadoxine–pyrimethamine with amodiaquine offers distinct therapeutic advantages, but the lack of correlation between *in vivo* susceptibility to amodiaquine and *in vitro* susceptibility to pyrimethamine is supportive evidence in favour of the superiority of the combination. It has previously been pointed out that, even in the absence of cross-resistance, combination treatment may only delay the appearance of resistance to the component drugs if the resistance to each separate constituent is relatively rare (*13*). Although most infections among the children in the present study were resistant to amodiaquine, the proportion of amodiaquine-resistant parasites could not be assessed. It must also be taken into account, that in an area where malaria is endemic, the proportion of infections exposed to treatment is low, and that as long as combination therapy can be reserved for cases that are both clinically and parasitologically chloroquine resistant, only a very small proportion of the parasite pool will be exposed to such therapy.

A controlled trial of sulfadoxine–pyrimethamine versus amodiaquine + sulfadoxine–pyrimethamine in a sufficiently large series of symptomatic patients is warranted. If the triple combination proves superior, it would be more rational to administer sulfadoxine–pyrimethamine on the first day instead of on the third day, as here, since it acts more rapidly than amodiaquine. Recent reports suggest, however, that prophylaxis with amodiaquine + sulfadoxine–pyrimethamine may be associated with severe side-effects (*14*). Nevertheless, in Maputo, more than 1000 patients have been treated with this combination and followed up for 28 days, and, apart from pruritus, dermatological or haematological side-effects have never been observed. However, in holoendemic areas it may often be necessary to treat children for malaria at intervals of 1–2 months, and determination of the risk of severe side-effects associated with repeated amodiaquine + sulfadoxine–pyrimethamine treatment must be considered a research priority.

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RÉSUMÉ

ÉVALUATION DE QUATRE SCHÉMAS THÉRAPEUTIQUES DANS LE PALUDISME À FALCIPARUM AU MOZAMBIQUE, 1986

Pour vérifier si l'association amodiaquine plus sulfadoxine/pyriméthamine conserve son efficacité thérapeutique malgré une résistance possible de *Plasmodium falciparum* à chacun de ses constituants, on a effectué une étude randomisée de l'effet de quatre traitements sur la parasitémie à *P. falciparum*. La population à l'étude consistait en 200 écoliers asymptomatiques du district de Machava, Maputo, Mozambique, secteur où la chloroquinorésistance a été fréquemment rapportée en 1985. De mai à septembre 1986, alors que la transmission du paludisme était à un niveau très faible, 50 enfants asymptomatiques présentant une parasitémie simple à *P. falciparum* asexué d'au moins 800 parasites par μl de sang ont été répartis dans chacun des quatre groupes thérapeutiques suivants: 25 mg/kg de poids corporel de chloroquine sur trois jours, 25 mg/kg d'amodiaquine sur trois jours, (25 + 1,25)mg/kg de sulfadoxine/pyriméthamine en une seule dose, et 25 mg/kg d'amodiaquine sur trois jours + (25 + 1,25)mg/kg de sulfadoxine/pyriméthamine le troisième jour. Au moment de commencer le traitement, des prélèvements de sang ont été réalisés et les microtests normalisés OMS de maturation des schizontes pour la détermination de la sensibilité à la chloroquine et à l'amodiaquine ont été effectués ainsi qu'une épreuve de 48 heures de réinvasion par les mérozoïtes pour la détermination de la sensibilité à la pyriméthamine. Dans la règle, les enfants ont été suivis au moyen d'épreuves *in vivo* pendant 35 jours à compter du début du traitement.

Chez les enfants étudiés, 94% des infestations étaient résistantes à la chloroquine *in vivo*, 76% à l'amodiaquine et 16% à la sulfadoxine/pyriméthamine. Dans tous les groupes, la résistance était surtout de degré RI. Le taux de guérison était de 100% avec l'amodiaquine + sulfadoxine/pyriméthamine (22 cas) mais ne différait pas sensiblement du taux obtenu avec la sulfadoxine/pyriméthamine seule. Parmi les traitements étudiés, la sulfadoxine/pyriméthamine avait l'effet le plus rapide (temps moyen de disparition des parasites: 1,85 jour), et tous les traitements entraînaient une augmentation de l'indice gamétocytaire, qui atteignait son maximum autour des jours 7 et 8. Les résultats des épreuves *in vitro* ont montré que 93% des enfants traités présentaient une chloroquinorésistance (concentration minimale inhibitrice $\geqslant 1{,}6$ μmol/l). En revanche, seuls 35% des enfants traités par l'amodiaquine présentaient une résistance *in vitro*; la différence entre les résultats des épreuves *in vivo* et *in vitro* (75,8%) pourrait être due à une réinfestation ou à des facteurs pharmacocinétiques.

Comme dans les études précédentes, une CI_{50} de pyriméthamine dans du RMPI 1640 supérieure ou égale à 3 μmol/l était associée à une résistance *in vivo* à la sulfadoxine/pyriméthamine. Il n'y avait pas de corrélation entre la sensibilité à la pyriméthamine *in vitro* et la sensibilité à l'amodiaquine *in vivo*.

Comme la résistance à l'amodiaquine est fréquente dans la région étudiée, ce médicament ne semble pas convenir pour remplacer la chloroquine. Il n'est cependant pas invraisemblable que l'effet thérapeutique de l'association amodiaquine + sulfadoxine/pyriméthamine soit supérieur à celui de la sulfadoxine/pyriméthamine seule, mais cette hypothèse devra être vérifiée lors d'un essai contrôlé randomisé portant sur des malades symptomatiques. La possibilité d'utiliser l'association pour retarder l'apparition d'une résistance plus fréquente aux deux constituants est examinée. L'article conclut que la sulfadoxine/pyriméthamine doit être administrée au début du traitement car elle agit plus rapidement que l'amodiaquine. On souligne également la nécessité d'étudier d'éventuels effets secondaires associés à la répétition de traitements par l'association triple.

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