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STUDY ON THE EFFECT OF FOUR DIFFERENT TYPES OF SINGLE DOSE  
ADMINISTRATION WITH CHLOROQUINE AND WITH CHLOROQUINE AND PYRIME-  
THAMINE ON PLASMODIUM FALCIPARUM INFECTIONS IN A SEMI-  
IMMUNE POPULATION IN NORTHERN NIGERIA

INDEXED

by

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1. Introduction and objectives

The single dose treatment of malaria is often employed in tropical Africa for reducing morbidity and mortality due to malaria. However, the drugs employed, subject to local availability, and the dosages used for attaining these aims differ from country to country (Lupascu, 1965) and seldom have preliminary trials been carried out under local conditions to evaluate the therapeutic values of these drugs and dosages in the different age-groups of population.

The present trial was undertaken in a savanna area of Northern Nigeria where malaria is hyperendemic, to assess the response of Plasmodium falciparum infection to four types of single dose treatment with chloroquine alone or with pyrimethamine, which are currently employed or might be used in the treatment of a semi-immune African population.

As in this area, there was virtually no transmission during the time of the trial, it was also possible to assess the suppressive as well as the apparent "radical cure" effect obtained after the single dose treatment. In this context, "radical cure" means that there was no reappearance of P. falciparum trophozoites in the peripheral blood, after the initial clearance following treatment and up to day 60. All previous field trials on the effects of single dose treatment with the exception of those of Clyde (1961) were carried out in areas where the risk of reinfection was constant and therefore only the initial response of the infection to treatment could be assessed with certainty.

2. Method

2.1 Selection of area and villages

In a savanna type area in the Province of Katsina (near Kankiya town), North Central State, the villages of Koda, Fakuwa and Tama, with a total population of 1935 people, located in the driest parts of this area were selected for the trial. The crude parasite rates (children two to nine years) at the commencement of the trial were respectively 60.0%, 76.0% and 60.5%.

Previous parasitological surveys showed that, in this area, malaria was stable with a high prevalence of P. falciparum (about 97%) followed by P. malariae and P. ovale.

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## 2.2 Epidemiological situation in the villages at the time of the trial

The trial took place from March to the end of May 1969, during the hottest part of the dry season when surface water was reduced to a minimum. Adult and larval densities regularly assessed in the village areas during the trial were so low that malaria transmission could hardly be expected. The probability of malaria transmission taking place was even further reduced by weekly larviciding of all water collections within a radius of 2.5 km of each village recorded during a geographical reconnaissance. At the beginning of the trial, a single dose of chloroquine and pyrimethamine (adult dose 450 mg of chloroquine and 45 mg of pyrimethamine) was administered to all known positive cases in the population excluded from the experiment.

## 2.3 Selection of subjects for treatment

After a preliminary examination of blood samples (thick smear) taken from the entire population of Koda and Fakuwa, and from all children (1-16 years) of Tama, only the subjects found with P. falciparum trophozoites in their blood were selected. The persons selected in Koda and Fakuwa were divided into two groups (Group 1 and Group 4) of approximately the same size, age ranges and level of parasitaemia. The subjects selected in Tama were similarly divided into Groups 2 and 3.

## 2.4 Drug administration and follow-up observations

In Groups 1, 2 and 3 the dosages of chloroquine base administered alone were adjusted respectively to body weight range (Group 1) surface area of subject (Group 2) and to standard dosage related to age-group (Group 3). In Group 4 a combination of chloroquine diphosphate and pyrimethamine was given at a standard dosage in relation to age.

The drugs and groups of dosages were employed as indicated in following tables:

Group 1		Group 2	
Dose (mg base chloroquine) adjusted to weight	Body weight range (kg)	Dose (mg base chloroquine) adjusted to surface area	Body weight (kg)
600	51-60	600	51-60
500	41-50	530	41-50
400	31-40	460	31-40
300	21-30	380	21-30
200	11-20	290	11-20
100	5-10	180	5-10

Group 3		Group 4		
Dose (mg base chloroquine)	Age-groups	Dose (mg base)		Age-groups
		Chloro- quine	Pyri- methamine	
150	3 months - 3 years	75	7.5	3 - 11 months
300	4 - 9 years	150	15	1 - 3 years
450	10 years and over	300	30	4 - 9 years
		450	45	10 years and over

The dosages in Group 2 are those suggested by a WHO Scientific Group on Resistance of Malaria Parasites to Drugs.<sup>1</sup>

The dosages in Group 3 are those recommended in the report of the Technical Meeting on Malaria Eradication<sup>2</sup> and those in Group 4 were used in a WHO field research project in 1966-1968 in Northern Nigeria.

Prior to treatment, solid food (biscuits) was given to each subject. The drug was swallowed with water and its ingestion carefully checked. Haskin's test for assessing the presence of chloroquine in the urine was carried out on samples collected in Tama from every child of two to four years old and from every person who had diarrhoea at the time of the drug administration.

Treatment took place on day "0" and thereafter blood films were taken daily from all subjects on days 1-5, every five days from days 5 to 30, and then every 10 days until day 60. The presence or absence of diarrhoea and vomiting two to three hours after treatment and within 12 hours thereafter, was noted.

### 2.5 Blood examination

The thick smears stained with Giemsa were examined for 20 minutes. During this time, about 400 microscopic fields containing each an average of 10-15 leucocytes, were examined. In order to calculate the density of asexual parasites and of gametocytes per mm<sup>3</sup>, trophozoites and/or gametocytes were counted against 500 leucocytes on the basis of an expected average number of 8000 leucocytes per mm<sup>3</sup> of blood.

### 2.6 Importance of prolonged examination of blood slides

The blood examinations in the course of this trial were of 20 minutes each (approx. 400 fields). This was demanded by the frequent very scanty residual parasitaemia, that an examination of five minutes (100 fields) would have often left undetected.

This is borne out by a series of observations.

The recording of results of microscopic examination for villages Koda and Fakuwa was made after 5, 10, 15 and 20 minutes. Thus, out of 566 slides found positive after 20 minutes of examination, only 22% were detected after five minutes of examination, 15% after 10 minutes and 75% after 15 minutes.

## 3. Results

Out of 522 P. falciparum carriers initially selected for treatment 425 were retained throughout the trial, the others being discarded for reasons such as absence for more than two successive examinations, for receiving unspecified treatment, for vomiting within two hours after taking the drug, for spitting out the drug, etc.

The effects of treatment on those followed from days 0 to 60 are summarized in Table 1.

In all four groups, on day 3, the parasite rates declined to levels of between 3.3 and 7% and on day 5 represented only between 1.3% and 3.4% of the original 100% level.

The mean clearance time of trophozoites in children (1-9 years) in each of the four groups was similar but in every case, longer than the one observed in the older age-group.

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<sup>1</sup> Wld Hlth Org. techn. Rep. Ser., (1965) 296, (Annex 3).

<sup>2</sup> Report of the Technical Meeting on Malaria Eradication in Africa, unpublished WHO working document AFRO/MAL/4, 1959.

Although the difference in clearance time between light and heavy infections is not statistically significant in each individual group (aged 1-9), this becomes significant if one pools together all the groups, in the sense that the mean duration of parasitaemia of all originally heavy infections in all the 1-9 year age-groups is longer (0.5 days) than the mean duration of all light infections.

Two subjects found positive continuously for at least the first six examinations, and those who missed on one or more examinations between day 1 and day 5 were not included in the calculation of the mean clearance time.

It is worth noting that percentages of recrudescences among subjects with diarrhoea (10.8%) at the time of medication is slightly higher than among those without diarrhoea (7.1%) and that in age-group 14 and above, recrudescences were less in Group 1 (4.1%) than in Group 4 (9.7%), in which the adult dosage was limited to a standard 450 mg of chloroquine-base.

Out of 32 detected cases that became again positive between day 10 and day 60, malaria parasites were found on only one occasion in 21 of them, and twice in two cases. In all these cases the parasitaemia was extremely low and often the diagnosis was made on a single parasite found after a long search. Of the remaining nine cases, the parasitaemia continued from day 5 in two of them, and in the other seven parasitaemia reappeared on days 15-20 and persisted almost continuously until day 60.

In six persons in Koda village continuing to show asexual parasites on day 10, but discarded from the trial as they had not received the appropriate dose of drug (but still more than 10 mg of base per kg of body weight), the second stage of the WHO field test for determining the strain sensitivity to a standard dose of chloroquine was carried out.<sup>1</sup> In all cases, parasites disappeared from the blood within the first two to three days after treatment.

Following drug administration, the gametocyte rates increased in all groups, but the rise in age-group 14 and above was less pronounced. The average gametocyte rate for all the children under 10 years increased from 13.0% to 29.0% within a week after the treatment and was still considerably higher than initially in all groups on day 15. In the group of children who received a single dose of chloroquine and pyrimethamine the rise of the gametocyte rate was less than in the other three groups. In 266 cases where no trophozoites were found after day 5, it was still possible to find gametocytes on day 30 (six cases) and on day 60 (one case). The gametocyte density index from day 2 to day 10 remained nearly at the same level and after day 10 it gradually fell.

### 3.1 Side effects

No side effects other than vomiting were reported. Vomiting was only observed in young children (below three years), except in Group 2, where children up to six years were affected.

The percentage of children that vomited within two hours after the treatment was 2.5% for Group 1, 8.0% for Group 2, 4.4% for Group 3 and 4.5% for Group 4.

## 4. Discussion

The trial, carried out in a savanna area of Northern Nigeria took place during a period and under conditions in which malaria transmission could be excluded. The dosages of chloroquine, with the exception of adults in Group 4, were in many cases higher than the 10 mg base/kg body weight normally used in field trials. The peripheral blood was not cleared of trophozoites on day 5 in seven children aged 1-9 years (2.4%) and in three persons 10 years of age and over (2.2%).

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<sup>1</sup> Wld. Hlth Org. techn. Rep. Ser. (1965) 296, pp. 37-38.

The parasite rates on day 5 were comparable with those observed by Lelijveld (1970) but lower than those reported by Bruce-Chwatt (1951), Shute & Dowling (1966) and Beausoleil (1968); probably due to the fact that most of the infections in the present trial were not recently acquired infections. It should also be noted that 400 microscopical fields were examined as compared to 100-200 fields examined by the first three authors quoted above.

In all groups of children, the mean clearance time tended to be just over 2.0 days whilst in adults it was 2.0 days or less even though the dosages of chloroquine base per kg of body weight were generally higher for children than for adults. Clyde (1961) and Lelijveld (1970) also observed a mean clearance time in adults below 2.0. In this trial, the mean clearance time was longer in the group of heavy infections than in the group of light infections which corresponds with the findings of Charles (1958).

It was observed that a single dose treatment with chloroquine, in dosages of 10 mg base/kg body weight or higher failed to prevent the reappearance of parasites within two months of treatment in 6.5-11.1% of the children in the 1-9 year age-group. These results are at variance with those reported by Clyde (1961) on 12 African children who after a single dose treatment of chloroquine and during a follow-up for three months in an area where malaria transmission was not occurring did not show recrudescences; however neither the number of follow-up examinations nor the number of microscopical fields examined were stated.

In almost all cases in which parasitaemia was discovered between day 10 and 60 after administration of chloroquine, parasites were found only once or twice and always in very small numbers. Slightly better results were observed in the group of children treated with a combined single dose of chloroquine and pyrimethamine. This may be due to the longer persistence of pyrimethamine in the blood, which may also account for the late reappearance of parasites (20 days or more after treatment) - in those cases where this occurred - compared with the groups treated with chloroquine alone in which parasites reappeared in the peripheral blood usually 10-20 days after treatment.

An increase in the gametocyte rates above the initial level during the first two to three weeks following a regular three-day course of treatment had already been noticed by authors. A rise in the gametocyte rates after the administration of a single dose treatment was observed by Charles (1958) although Miller (1954) and Shute & Dowling (1966) observed a steep fall in gametocyte rates after treatment with chloroquine. In our trials the rise of gametocyte rates after the administration of any type of single dose treatment occurred in all age-groups. The presence of gametocytes in the blood of semi-immunes 60 days after treatment, in the absence of asexual parasitaemia, may be of epidemiological importance. While comparing the results of the present trial with others attention should be paid to the fact that in previous trials of the same type (Bruce-Chwatt, 1951; Charles, 1958; Clyde, 1961; Lelijveld, 1970; Miller, 1954 and others) the number of microscopical fields examined varied from 100 to 200 and this according to present observation, may reveal only some 45% of the total number of positives that could be found after a 20 minute examination.

Side effects, such as vomiting, were observed in between 2.5 and 4.5% of the children below three years in Groups, 1, 3 and 4. In Group 2 where dosages were adjusted to surface area and were as a rule higher than in the other groups, the percentage of subjects (up to 6 years) who vomited two hours after the treatment was as high as 8%. In Group 4, where the dosage was the same as in a trial carried out in 1967-1968 in Kankiya district, but in which it was administered after ingestion of a biscuit, the percentage of subjects vomiting was half that reported in Kankiya (9%). (Najera, 1968 unpublished report to WHO).

TABLE 1. EFFECTS OF FOUR DIFFERENT TYPES OF SINGLE DOSE TREATMENT WITH CHLOROQUINE (GROUPS 1, 2 AND 3) AND CHLOROQUINE PLUS PYRIMETHAMINE (GROUP 4) ON P. FALCIPARUM INFECTIONS IN SEMI-IMMUNE SUBJECTS

Age-group	Group 1		Group 2		Group 3	Group 4	
	1-9	14 +	1-9	10-16	1-9	1-9	14 +
Number of cases followed up from day 0 to day 60	79	49	77	24	45	89	62
Parasite rate							
On day 3	6.4	6.1	5.2	4.2	7.0	4.6	3.3
On day 5	1.3	2.1	2.6	0.0	2.3	3.4	3.3
Mean clearance time (days)	2.08	1.7	2.18	2.0	2.25	2.0	1.5
Mean clearance time (days) of heavy infections*	2.3		2.5			2.5	
light infections**	2.0		2.2			1.9	
Percentage of cases relapsing between day 10 and day 60	7.6	4.1	6.5	0.0	11.1	6.9	9.7

\* Above 1000 falciparum trophozoites per mm<sup>3</sup> of blood.

\*\* Below 1000 falciparum trophozoites per mm<sup>3</sup> of blood.

##### 5. Summary and conclusions

All the four types of treatment with dosages of 10 mg chloroquine base per kg of body weight or above proved by and large to be equally effective in all age-groups as regards rapid reduction of parasite rates, parasite clearance time and reduction of parasite density.

In the absence of transmission, the reappearance of trophozoites between days 10 and 60 after single dose treatment was detected in 4.7% to 11.1% cases in the course of one or more of eight follow-up blood examinations of 20 minutes each (400 microscopical fields). In general the trophozoites reappeared more frequently in children than in adults except in the Group 4 where a combined dosage of chloroquine and pyrimethamine was used and where the dosage of chloroquine given to adults weighing more than 45 kg was less than 10 mg base per kg of body weight.

The necessity of prolonged examination of each blood film in trials of drugs, included as one of the objectives is the assessment of "radical cure effect", is stressed by the fact that routine five minute examinations usually employed in a trial of this type reveal only 22% positive, out of a total of 100% detected in a 20 minute examination.

A considerable rise in the falciparum gametocyte rates for three weeks, was consistently observed after a single dose treatment with chloroquine indicating the need of supplementing this drug with gametocytocides in projects aiming at reduction of malaria transmission.

The percentage (8%) of side effects (vomiting) observed in children given a single dose of chloroquine adjusted to surface area of the body makes this type of dosage using uncoated tablets unsuitable under field conditions.

Dosages of chloroquine adjusted to body weight range would appear preferable and could be used by health posts and in mass drug administration schemes covering selected groups of population. When using a standard treatment in relation to age, a single dose of 600 mg base for persons above 16 years would appear to be desirable, except for ethnic groups of slight build.

## RESUME

Entre mars et mai 1969, c'est-à-dire au cours de la période où la transmission du paludisme est pratiquement nulle, on a étudié au sein d'une population semi-immune de trois villages situés dans l'Etat centre-nord du Nigéria les effets qu'exercent les infections à Plasmodium falciparum des traitements comportant une dose unique de chloroquine fixée en fonction soit du poids corporel, soit de la surface du corps, soit de l'âge des sujets, ou d'une dose unique de chloroquine et de pyriméthamine associées. Quatre cent vingt-cinq personnes de divers âges ont été suivies pendant 60 jours et l'examen d'une goutte épaisse de sang pendant 20 minutes a été pratiqué pour chacune d'elles 12 à 13 fois après l'administration du médicament. Sur le total des cas qui ont été trouvés positifs à l'origine, 22 % ont été décelés après 5 minutes d'examen d'une goutte épaisse, 45 % après 10 minutes, 77 % après 15 minutes et 100 % après 20 minutes.

Les quatre types de traitement, qui représentaient une dose de 10 mg ou plus de chloroquine-base par kg de poids corporel, se sont révélés dans l'ensemble très efficaces pour tous les groupes d'âge en ce sens qu'ils ont permis une réduction rapide de l'indice plasmodique et du délai de disparition des parasites, ainsi qu'une diminution de la densité parasitaire. Entre le dixième et le soixantième jour qui ont suivi l'application du traitement à dose unique, on a noté la réapparition de trophozoïtes dans un groupe représentant entre 4,7 % et 11,1 % des cas suivant le type de traitement ou le groupe d'âge; deux cas n'ont pas pu être élucidés. Pendant les trois semaines qui ont suivi l'administration de la dose unique, on a régulièrement observé une augmentation considérable de l'indice gamétocytaire, sans augmentation de la densité gamétocytaire.

En raison du pourcentage (8 %) d'effets secondaires (vomissements) observés chez les enfants auxquels on avait administré une dose unique de chloroquine ajustée en fonction de la surface du corps, ce type de traitement, pour lequel on utilise des comprimés non enrobés, ne saurait être appliqué sur le terrain.

Il semblerait préférable d'adopter des doses de chloroquine ajustées en fonction du poids corporel, qui pourraient être utilisées dans les postes sanitaires et se prêteraient à la chimiothérapie de masse dans certains groupes de population. Si l'on adoptait un traitement uniforme ajusté en fonction de l'âge, il serait souhaitable de choisir une dose unique de 600 mg de chloroquine-base pour les personnes de plus de 16 ans, sauf dans le cas des groupes ethniques de petite stature.

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