

4-Aminoquinoline Prophylaxis of Malaria amongst Semi-Immune African School Children

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Drugs used for the prophylaxis of malaria are generally recommended in doses sufficient to suppress the disease in persons without immunity, these amounts being considerably in excess of those required for the protection of indigenous inhabitants of malarious districts. Information is not generally available concerning the smallest useful doses of the 4-aminoquinoline series of suppressives amongst school children who possess a high degree of premunition, because treatment varies from place to place in relation to differing degrees of immunity and infection risk.

It is the purpose of the trials described in this report to demonstrate dosages of amodiaquine and chloroquine just sufficient to prevent overt parasitaemia in children aged 6 to 15 years native to areas of holoendemic malaria transmission in East and Central Africa where *Plasmodium falciparum* predominates.

METHOD: THE SUBJECTS AND THE DRUGS

Apparently healthy African children attending three schools near Muheza, in north-east Tanganyika, were treated at the commencement of this investigation with a single large dose of the appropriate 4-aminoquinoline in order to remove existing parasitaemia. Four days later the first of the prophylactic treatments was administered, some of the children being excluded for purposes of contrast. The children lived in an area of malarial holoendemicity described previously by Davidson and Draper (1953), the relevant parasite rates found by ourselves being:

| Age | Parasite Rate |
|-------|---------------|
| 0-2 | 76 |
| 3-5 | 88 |
| 6-10 | 82 |
| 11-15 | 63 |
| Adult | 24 |

The most prevalent species, *Plasmodium falciparum*, was present in 98 per cent. of positive slides of children aged 6 to 15, *P. malariae* in 4 per cent. and *P. vivax* in 1 per cent.

The drug dosage used for initial parasite suppression was 0.6 gm. amodiaquine or chloroquine base, adult dose, modified according to the age of the child. Following this treatment, the blood was cleared of parasites. In the unprotected control cases parasitaemia recurred within eight weeks. The remaining children received, under our direct supervision, the prophylactic doses divided into four schedules for each of

Table I

PROPHYLACTIC TRIALS WITH AMODIAQUINE AT TWO-WEEK INTERVALS

| Schedule | Age 6-8 | Age 9-10 | Age 11-12 | Age 13-15 |
|---------------------|---------|----------|-----------|-----------|
| A1: dose (gm. base) | 0.15 | 0.15 | 0.2 | 0.25 |
| Number examined | 8 | 21 | 17 | 20 |
| Number reinfected | 0 | 1 | 0 | 0 |
| A2: dose | 0.1 | 0.1 | 0.15 | 0.2 |
| Number examined | 25 | 30 | 26 | 15 |
| Number reinfected | 0 | 0 | 0 | 0 |
| A3: dose | 0.05 | 0.05 | 0.1 | 0.1 |
| Number examined | 27 | 35 | 36 | 19 |
| Number reinfected | 7 | 6 | 0 | 0 |
| A4: dose | 0.025 | 0.025 | 0.05 | 0.05 |
| Number examined | 15 | 13 | 27 | 20 |
| Number reinfected | 8 | 6 | 2 | 1 |

the two drugs. These schedules were calculated from the adult dose using Young's formula, to the nearest one-eighth tablet, powdering not being practicable on account of bitterness. Blood examinations were limited to the untreated children and to those receiving the drugs fortnightly for a period of 8 to 12 weeks without defaulting, and were made at the end of a two-week period.

RESULTS OF FORTNIGHTLY DRUG PROPHYLAXIS

Amodiaquine.—Four graduated schedules of dosage of amodiaquine were used. The first, A1, corresponding to 0.4 gm. adult dose, was related to that recommended by Covell, Coatney, Field and Jaswant Singh (1955) for non-immune subjects, but was given at intervals of two weeks. The schedules A2, A3 and A4 were progressively less, corresponding to adult doses of 0.3, 0.2 and 0.1 gm. The dosages and the results of blood examinations performed following 8 to 12 weeks of treatment are shown in Table I.

It appears from Table I that under the conditions of premunition existing amongst the school children, and following upon clearance of blood parasites, amodiaquine at a fortnightly dosage of 0.1 gm. was sufficient to prevent recurrence of parasitaemia despite the high rate of transmission prevailing.

Chloroquine.—Four schedules of dosage of chloroquine diphosphate were also used, the first, C1, corresponding to 0.3 gm. base adult dose, being that recommended for non-immunes, but administered at fortnightly intervals. The schedules C2, C3 and C4 corresponded to adult doses of 0.225, 0.15 and 0.075 gm. respectively. The dosages expressed as chloroquine base, for three-quarter, quarter and one-eighth tablets reduced to two decimal places, are shown in Table II.

These results for chloroquine indicate that a fortnightly dosage of 0.075 gm. base prevented a recurrence of parasitaemia following initial blood clearance.

PARASITE DENSITIES

At the largest dosages through which parasites reappeared the densities remained in most cases low, less than 100 per c.m. blood, irrespective of age of child. Many of these parasites were damaged. At the next lower schedule densities were considerably higher and parasites stained normally in films from younger and less immune children. All the positive slides contained *P. falciparum* and two also were seen to have

P. malariae, these latter being at the lowest chloroquine dosage in children aged 8 to 10.

The single case of break-through on the highest amodiaquine schedule could not be explained, but was in such low density that only one asexual ring was found. The child concerned was a lifelong resident of the district and differed in immunity in no manner from his fellows.

DISCUSSION

The amount of amodiaquine found by ourselves to be just sufficient to prevent parasitaemia, 0.1 gm. given once every two weeks, may be compared with the findings of other workers. Authors in India and Malaya have recorded amodiaquine dosages of 0.4 gm. administered fortnightly as being suitable for indigenous children living in endemic districts, for one group aged less than 12 years half that amount offering considerable protection. In Africa, Fabre and Joigny (1955) in French Equatoria have found, for amodiaquine in highly endemic areas, 0.4 gm. suitable at intervals of two weeks in the prophylaxis of malaria in children aged 6 to 12; and de Smet (1952) has given monthly treatments in the Belgian Congo at the rate of 25 mg. per kilo. body weight to children aged up to 12 years, this being from three to five times the minimal protective dose recorded by ourselves. At weekly intervals Miller (1954) in Liberia found 0.2 gm. effective in children aged 6 to 14, although an occasional temporary break-through took place.

The amount of chloroquine, 0.075 gm., used by us every two weeks may also be compared. Doucet (1947) found in the Congo in areas of high endemicity, 0.125 gm. weekly was completely protective for children aged six to seven; and Rule (1951), using weekly doses of the diphosphate following initial eradication therapy, recommended for the effective suppression of malaria 0.25 gm. (one tablet) in children aged less than 10 years, and 0.375 gm. in those from 10 to 15. These doses appear, however, to have been expressed not in base but in salt, and should probably read 0.15 and 0.225 gm. base respectively. Also Miller (1954) used 0.15 gm. base chloroquine at weekly rates with effective suppression of malaria in children aged 6 to 14.

It therefore appears, following initial blood clearance, that the quantities of the two drugs found by ourselves to prevent recurrence of parasitaemia are from one-half to one-quarter those recommended elsewhere for school child-

Table II
PROPHYLACTIC TRIALS WITH CHLOROQUINE AT TWO-WEEK INTERVALS

| Schedule | Age 6-8 | Age 9-10 | Age 11-12 | Age 13-15 |
|---------------------------|---------|----------|-----------|-----------|
| C1: dose (gm. base) | 0.11 | 0.11 | 0.15 | 0.19 |
| Number examined | 19 | 23 | 22 | 17 |
| Number reinfected | 0 | 0 | 0 | 0 |
| C2: dose | 0.075 | 0.075 | 0.11 | 0.15 |
| Number examined | 27 | 22 | 33 | 32 |
| Number reinfected | 0 | 0 | 0 | 0 |
| C3: dose | 0.04 | 0.04 | 0.075 | 0.075 |
| Number examined | 30 | 46 | 35 | 33 |
| Number reinfected | 6 | 4 | 0 | 0 |
| C4: dose | 0.02 | 0.02 | 0.04 | 0.04 |
| Number examined | 17 | 26 | 31 | 26 |
| Number reinfected | 8 | 9 | 8 | 2 |

ren native to districts where malaria is endemic and the inhabitants semi-immune. It appears likely, moreover, that the initial blood clearance treatment is unnecessary, the prophylactic doses themselves sufficing to clear parasites. Marginally effective dosages such as these are obviously insufficient for the protection of non-immune subjects, although with the 4-aminoquinolines the hazard of drug resistance need not be feared. The most serious objection to the use of any fortnightly treatment is that, in the event of a dose being missed, parasitaemia may ensue before the next dose falls due; on practical grounds, therefore, the weekly administration of 0.1 gm. amodiaquine or 0.075 gm. chloroquine base to semi-immune children is preferable.

SUMMARY

An investigation is reported concerning the smallest effective prophylactic doses of 4-aminoquinolines used amongst African school children aged 6 to 15 years native to areas of malarial

holoendemicity in Tanganyika. Fortnightly doses of 0.1 gm. amodiaquine and 0.075 gm. base chloroquine prevented recurrence of parasitaemia over a period of 8 to 12 weeks.

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Acknowledgment

We are indebted to the Honourable the Director of Medical Services, Tanganyika, for permission to publish these observations.