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FIELD TRIALS OF SOME NEW ANTIMALARIAL COMPOUNDS

by

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Introduction

Over a number of years a series of evaluations of antimalarial drugs has been carried out by the Federal Malaria Service of Nigeria by which the respective merits of proguanil, mepacrine and chloroquine (Bruce-Chwatt, 1951), pyrimethamine (Archibald, 1951), "Azacrin" and "Camoquin", amodiaquine (Bruce-Chwatt & Archibald, 1953; Charles, 1958) have been assessed by a method evolved in Nigeria, (Bruce-Chwatt, 1951). That method was also used to demonstrate the value of one of a series of hydroxynaphthalenes (Bruce-Chwatt & Charles, 1957 (a)) and to show the relatively limited value of chloroquine naphthoate (Bruce-Chwatt & Charles, 1957 (b); Clyde & Shute, 1958), and it has been used to determine the relative efficiency of different routes of administration (Bruce-Chwatt & Gibson, 1959). The present investigation made use of the method to determine the value of single dose treatment with (a) "Lapudrine", (3:4 - dichlorophenyl-isopropyl-diguanide hydrochloride), a drug very similar in its properties to proguanil but more persistent and effective at a low dosage (Robertson, 1957), (b) of a new compound - chloroquine tannate and (c) of coated pills of chloroquine diphosphate. The two chloroquine preparations were developed in an attempt to produce a tasteless preparation of chloroquine to overcome the objection met with when administering the bitter chloroquine tablets at present marketed. Current preparations of pyrimethamine and of chloroquine phosphate were used for comparison.

Method of investigation

A preliminary investigation was made of school and village children at Mungadi and Suru in Western Sokoto, Northern Nigeria, to determine the occurrence of splenomegaly and parasitaemia among the children. One hundred and forty-three children between the ages of 5 and 11 years showing trophozoites of P. falciparum in their blood were selected and distributed into six groups so arranged as to be comparable in age-composition and in densities of parasitaemia, and reasonably comparable in spleen rate. The parasite densities were determined from the parasite-leucocyte ratio in thick blood films stained with Giemsa, and classified into one of ten geometrically progressing density classes (Bruce-Chwatt, 1958); splenomegaly was classified according to Hackett's system. The composition of the groups is shown in Table 1.

TABLE 1. COMPOSITION OF GROUPS OF CHILDREN SELECTED FOR THE INVESTIGATION

Group	1	2	3	4	5	6
Number in group	23	25	22	26	26	21
Mean age	7.4	7.6	7.8	7.6	7.3	7.6
Std. Deviation	+1.8	+1.5	+1.4	+1.2	+1.5	+1.7
Spleen Rate	59.1	66.7	66.7	46.1	58.3	60.0
Average Enlarged Spleen	1.8	1.7	1.8	1.8	1.7	1.9
Parasite Density Index	2.91	3.30	2.78	3.15	1.89	2.71

The "Lapudrine" used in the present investigations was dispensed as white tablets of 20 mg each, rather bitter to the taste, but small enough to be easily swallowed. The effect of the 20 mg dose was compared with that of the common 25 mg tablet of "Daraprim" (pyrimethamine).

The coated pills of chloroquine diphosphate each contained 375 mg of chloroquine base. There were small, glossy-white pills rather smaller in size than "Daraprim" tablets and so even easier to swallow. They are completely tasteless unless broken by biting when the bitter chloroquine phosphate can, of course, be tasted.

The chloroquine tannate was dispensed as tablets each containing 75 mg of chloroquine base. They were off-white tablets, larger than the commercial tablets of chloroquine although only containing half their content of chloroquine base. They were much less bitter than chloroquine phosphate but were not tasteless.

These two experimental chloroquine preparations were compared with commercial tablets of chloroquine diphosphate, all three preparations being administered to give a dose of 300 mg of chloroquine base.

On the morning of D day, drugs were administered by us to the children in the five groups, the sixth group being used as a control. We ensured that every child had swallowed its dose. The children in group 1 received 25 mg pyrimethamine; in group 2, 20 mg "Lapudrine"; groups 3, 4 and 5 all received 300 mg chloroquine base; (group 3 in the form of chloroquine diphosphate, group 4 as chloroquine tannate and group 5 as coated pellets of chloroquine diphosphate). Group 6 was not treated. Parasitaemia was determined at intervals of 24 hours thereafter for five days; no slide was declared negative until 100 thick film fields had been examined. The results are shown in Table 2.

TABLE 2. EFFECT OF VARIOUS DRUGS GIVEN AT SINGLE DOSES  
ON P. FALCIPARUM TROPHOZOITE PARASITAEMIA

Treatment schedule	1 Pyrimethamine 25 mg	2 "Lapudrine" 20 mg	3 Chloroquine diphosphate 300 mg base	4 Chloroquine tannate 300 mg base	5 Chloroquine diphosphate coated pellets 300 mg base	6 Un-treated
Number in group	23	25	22	26	26	21
Number cleared within 24 hours	4	2	9	2	2	Nil
" 48 "	17	20	9	14	17	1
" 96 "	2	2	4	9	5	Nil
" 120 "	-	-	-	-	-	Nil
" 144 "	-	-	-	-	-	Nil
Mean clearance time	33.91 + 12 hrs	36.0 + 10 hrs	30.5 + 17.5 hrs	42.72 + 13 hrs	39.0 + 12.5 hrs	- -
Number with persisting parasitaemia	Nil	1	Nil	1	2	20
Parasite Density Index of group before treatment	2.91	3.30	2.78	3.15	2.89	2.71
After 24 hours	1.39	2.52	0.91	1.19	1.65	2.34
" 48 "	0.09	0.16	0.18	0.46	0.35	2.43
" 96 "	0.00	0.16	0.00	0.15	0.15	2.57
" 120 "	0.00	0.16	0.00	0.15	0.19	2.48
" 144 "	0.00	0.24	0.00	0.15	0.23	2.48

Advantages and disadvantages of the preparations used in this investigation:

Individuals vary in their ability to swallow pills; objection appears to arise on grounds either of the size of the pill, its taste or the number that have to be swallowed. The single small tasteless tablet causes least trouble. In the present investigation "Daraprim" and "Lapudrine" fell into this class and no difficulty was met in administering them to children 5-11 years old.

The coated chloroquine pellet was as small as these tablets and equally tasteless unless bitten, but its small content of chloroquine base (37.5 mg) led to the giving of eight tablets to obtain a dose of 300 mg. This causes trouble to poor swallows who then bit their pellets and lost the advantage of tastelessness.

The current commercial chloroquine salts have the major disadvantage of bitter taste. The tablet contains a substantial dose of chloroquine (150 mg) but is rather too large for easy swallowing. The less pronounced taste of the tannate does not compensate for the even greater size of its tablet and for the need to swallow twice as many tablets of that salt to achieve an equivalent dose of chloroquine base since each contains only half that contained in the commercial tablet (chloroquine diphosphate or chloroquine sulfate).

### Discussion

Forty-one (28.8%) of the 143 individuals investigated had mixed infections of P. falciparum and P. malariae and 5 (3.5%) showed P. ovale parasites at least once during the series of examinations. The two latter infections were all of low density even at the start of the investigation and apart from persistence of P. malariae gametocytes in 2 cases, they disappeared following treatment within 144 hours.

Ninety-two (64.3%) of the 143 individuals showed crescents of P. falciparum in the course of the investigation. The mean gametocyte rate at any single examination was 24.1%. Although the individuals in whom crescents were seen varied from day to day throughout the investigation, (only 4 children showing crescents on every examination), yet the group gametocyte density indices showed little variation from day to day, the mean being  $0.32 \pm 0.05$ . (This corresponds to a density of less than 100 per  $m^3$ ).

The value of the investigation rests on the consideration of the changes in the parasite rate and density of P. falciparum trophozoites following single dose treatment. Chloroquine diphosphate<sup>1</sup> with a clearance time of 30.5 hours and a 100% clearance rate was conspicuously better than either of the two chloroquine preparations the clearance times of which were 42.7 and 39.0 hours respectively; the 100% clearance rate was not achieved in these two groups. "Daraprim" and "Lapudrine" had very similar clearance times of 33.9 and 36.0 hours and again the latter drug did not achieve 100% clearance rate.

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<sup>1</sup> Editor's note: In this group the initial parasite density index was lowest.

The four cases of persistent parasitaemia are of great interest in throwing light on occasional failures in treatment and in pointing to a possible flaw in schemes of mass chemotherapy. Their trophozoite densities day by day are shown in Table 3. These appear likely to be due to failure of absorption since the "Lapudrine" case (No. 179) was cleared within 48 hours of receiving a second dose of that drug and one of the cases given coated chloroquine (No. 161) responded similarly to a second dose of chloroquine. The other two cases (Nos. 130 and 131) were sisters. They were not observed after re-treatment and so their response cannot be reported. However, we have noticed on other occasions similar persistence of parasitaemia following the administration of chloroquine sulfate and chloroquine phosphate and occasionally it has required repeated administrations to clear the parasitaemia in spite of evidence that the drug had certainly been swallowed. In the cases described above, there was no complaint of vomiting or of diarrhoea to explain a failure to absorb after swallowing. No excretion tests were performed.

TABLE 3. RECORD OF REFRACTORY CASES NOT CLEARED OF PARASITES WITHIN 144 HOURS AFTER A SINGLE ADMINISTRATION OF ANTIMALARIAL

Case	Drug administration	Parasite density indices				<u>P. falciparum</u> trophozoites only	
		Before admin.	After 24 hrs	After 48 hrs	After 96 hrs	After 120 hrs	After 144 hrs
179	"Lapudrine" 20 mg	1	3	2	4	4	6
130	Chloroquine tannate 300 mg base	3	Neg	3	4	4	4
131	Chloroquine diphosphate coated pellets 300 mg base	3	2	1	4	4	6
161	Chloroquine diphosphate coated pellets 300 mg base	5	5	3	Neg	2	2

Conclusion: From this investigation, "Lapudrine" seems to be a useful alternative to "Daraprim", against the erythrocytic stages of P. falciparum. This is, of course, an observation of limited importance since both those drugs are principally of interest as causal prophylactics.

For single dose treatment chloroquine tannate is certainly not as good an antimalarial as the diphosphate. In this investigation, two disadvantages far outweighed the modest benefit of its less pronounced taste; twice as many tablets of the tannate had to be swallowed to give an equivalent dose of base and even then a markedly slower clearance was observed. We see no point in complicating still further the antimalarial pharmacopoeia by introducing this compound.

The same objections in part apply to the small coated pellets. These are, however, designed for the special group of very young children and may well have a place in the treatment of that class of patient. They are certainly easily swallowed by all who can swallow a pill. The cost at which they are marketed might well determine the place they would come to occupy.<sup>1</sup>

### Summary

One new antimalarial preparation, "Lapudrine", and two experimental preparations, chloroquine tannate and coated chloroquine diphosphate, were tested alongside pyrimethamine ("Daraprim") and chloroquine diphosphate by observing their effect on trophozoite parasitaemia in groups of symptomless African schoolchildren.

It was observed that single doses of "Lapudrine" had much the same activity as "Daraprim" in this trial but that neither of the two experimental chloroquine preparations effected as quick a clearance of P. falciparum trophozoites as did tablets of chloroquine diphosphate.

Four cases of persistence of parasitaemia are discussed. Conclusions are drawn from the investigation that "Lapudrine" might be a useful alternative to "Daraprim"; there would be no benefit from putting chloroquine tannate on the market but that coated pellets of chloroquine diphosphate would have a field of usefulness in the treatment of young children and perhaps also some adults.

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<sup>1</sup> Editor's note: It should be possible to double the chloroquine content of the pellet (i.e. 75 mg base/pellet instead of 37.5 mg). At the same time the coating should be reduced in order to secure more rapid disintegration of the pellets.

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