

P. FALCIPARUM INFECTION IN CHILDREN: TREATMENT WITH A CHLOROQUINE-PYRIMETHAMINE SYRUP (DARAFLOR)

PRELIMINARY OBSERVATIONS

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An important part of the antimalaria campaign in the Northern Transvaal is an attack on the malaria parasites harboured by so-called 'symptomless carriers'. In 1962 a programme of mass blood examination, with treatment of positive cases, was organized by Dr. N. J. le Roux, of the State Health Department. It was not expected that this would entirely eliminate parasites in one malaria season, but it is felt that the organization set up should, by a process of attrition, eventually stop any significant transmission. Three factors militate against complete elimination, viz.:

1. A steady influx of malarial immigrants continues.
2. One blood examination does not discover more than a proportion of the positives.
3. The effectiveness of treatment is uncertain.

The problem of malarial immigrants is a difficult one. There are, broadly, 3 classes of immigrants, viz. (1) legal immigrants, who could hardly be welcomed to the Republic with a compulsory dose of chloroquine, (2) legally immigrated contract labour, who could be coerced into popping some tablets into their mouths—not the same as swallowing them—and (3) illegal immigrants.

Nor is it easy to overcome the inadequacy of single blood examinations. The people would not tolerate multiple blood examinations, and the staff required could not be found. There remains the problem of improving the treatment of parasite carriers discovered during the campaign, and this is the object of the present investigation.

PRESENT INVESTIGATION

If all positive cases discovered each year were completely rid of their parasites there would be good reason to expect a progressive reduction of parasitaemia to a point where significant transmission would cease. The drug hitherto in use was chloroquine, which had the obvious disadvantages that though it is schizonticidal it is neither gametocidal nor sporontocidal, and that it is most unpalatable. Of course, the schizonticidal action would prevent the development of gametocytes if the drug could be given early enough; but, as most positive cases were already showing gametocytes, it was useless to rely on a drug that could kill the plasmodium in the schizont stage only.

It was therefore decided to combine for use a schizonticide and a sporontocide, namely, chloroquine and pyrimethamine. The combination was available as 'daraflor' in tablet form. If absorption of the tablets were certain, one disadvantage of the single-action chloroquine would be overcome. With adults this can be achieved by using a tongue depressor after the tablets have been taken. It is different with infants and children. Short of a brutal assault that no parents would tolerate, it would take the

suave patience of a successful paediatrician to persuade powdered chloroquine down the spastic throats of retching, screaming infants. It would be unrealistic to expect a busy field worker to crouch in a kraal and carry this out. To get over this difficulty an attempt was made to incorporate the daraflor in a suspension. The insolubility of pyrimethamine made a suspension necessary. The ingredients were: powdered daraflor, pulv. trag. co., saccharin and syr. aurantii. The syrup was reasonably successful. It was 'lapped up' by children, and even infants did not give much trouble. It had been hoped to use it for adults also in order to avoid the buccal-examination technique, but the dilution necessary made the dose too bulky. In order to get adequate supplies the firm making daraflor was asked to try to evolve a practical syrup. A stable syrup was produced with a not unpleasant liquorice flavour. This syrup was readily taken by small children, and infants needed little persuasion. Unfortunately the adult dose is still too bulky. The trial was made with this syrup.

The blood examinations made numbered 4,296 and, of the 25 positives that were discovered, 16 children aged 3-12 years with gametocytes were selected. All had *P. falciparum* parasites only. The children were taken to hospital and kept under observation for 7 days. After 7 days in hospital, during which time daily blood smears—thick and thin—were prepared, the children went home. This was the 'off-season' with transmission at its lowest and, as expected, during the 35 days of the trial there were no reinfections.

On admission to hospital 7 of the children were given a 3-day course of treatment, and 9 of them a 1-day course. According to age, the following quantities of pyrimethamine and basic chloroquine were given in divided doses in the 3-day course (P=pyrimethamine, C=chloroquine):

Age (yrs.)	1st day (mg.)		2nd day (mg.)		3rd day (mg.)	
	P	C	P	C	P	C
Over 11 ..	60	600	30	300	30	300
6-11 ..	45	450	15	150	15	150
1-5 ..	30	300	7	70	7	70
Under 1 ..	15	150	7	70	7	70

The 1-day course was the same as the 1st day of the 3-day course, i.e., the 2nd and 3rd days were omitted.

The results of treatment are given in Tables I and II.

The degree of reliability of these results may be assessed by reference to the appendix to this report. Although only 16 cases were investigated it is submitted that the near-uniformity of the results makes them significant. The results are:

1. Rapid disappearance of trophozoites.
2. Reduction and eventual disappearance of gametocytes.

TABLE I. THREE-DAY TREATMENT

Day	Case 1 (M3)		Case 2 (F4)		Case 3 (M5)		Case 4 (M7)		Case 5 (M9)		Case 6 (F11)		Case 7 (F12)	
	R	G	R	G	R	G	R	G	R	G	R	G	R	G
Before treatment	++	++	++	+	+++	++	++	+	+	+	+	+	++	+
After treatment	+	++	++	+	+++	++	+	++	+	+	+	++	+	++
1	+	++	+	+	++	++	+	++	+	+	+	++	+	++
2	—	++	+	+	++	++	+	++	+	+	+	++	+	++
3	—	++	—	+	—	++	—	++	—	+	—	++	—	++
4	—	++	—	+	—	++	—	++	—	+	—	++	—	++
5	—	++	—	+	—	++	—	++	—	+	—	++	—	++
6	—	++	—	+	—	++	—	++	—	+	—	++	—	++
7	—	++	—	+	—	++	—	++	—	+	—	++	—	++
25	—	++	—	+	—	++	—	++	—	+	—	++	—	++
39	—	—	—	—	—	—	—	—	—	—	—	—	—	—

R (Ring) = trophozoite, G = gametocyte, O = 'disintegrated' gametocyte, + (see appendix).

TABLE II. ONE-DAY TREATMENT

Day	Case 8 (M3)		Case 9 (M4)		Case 10 (M5)		Case 11 (M6)		Case 12 (M10)		Case 13 (F10)		Case 14 (F10)		Case 15 (F12)		Case 16 (M13)	
	R	G	R	G	R	G	R	G	R	G	R	G	R	G	R	G	R	G
Before treatment	++	++	++	++	++	+	++	+	++	+	++	+	++	+	++	+	++	+
After treatment	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
1	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
2	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+
4	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+
5	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+
6	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+
7	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+
24	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
38	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

3. The results of 1-day treatment were at least as good as those of 3-day treatment.

4. An unusual form appeared which suggests disintegrating gametocytes. This form was found *only* in slides after treatment. It is being further investigated.

5. In 4 of the cases, numbers 2, 7, 11 and 14, gametocytes were found originally but could not be found 10 days later on admission to hospital. They reappeared after a few days.

6. The syrup was taken by the children without undue fuss and there were no side-effects and no nausea.

It may be noted that case no. 15 is the only one with an incomplete record. This 12-year-old girl left the district after the 24th day and could not be traced.

Temperature records are available for the first 2 days for the 9 patients who received 1-day treatment:

TEMPERATURES IN °F.

Case number	On admission	First day		Second day	
		Morning	Evening	Morning	Evening
8	98.4	98.4	98.6	99.0	99.0
9	99.6	99.0	98.6	98.6	98.0
10	100.0	99.4	99.0	99.6	100.0
11	99.2	98.8	98.4	98.4	98.6
12	100.0	99.4	99.4	99.0	98.4
13	99.0	98.4	98.4	98.8	99.6
14	99.4	99.0	98.8	98.4	98.0
15	100.2	100.0	99.0	98.0	98.4
16	98.0	98.4	99.0	99.8	99.0

There was no correlation between degrees of fever and density of parasites. It was interesting, however, that all of these 'symptomless carriers' were febrile at some time during these two days, and that 3 (33%) had temperatures of 100°F. or more on admission to hospital. This indifference to varying degrees of fever has been frequently noticed in Bantu parasite carriers and further investiga-

tions will have to be made to determine how many parasite carriers would be missed if only febrile bloods were examined. In this series it seems that only 2 out of 9 would have been missed.

DISCUSSION AND SUMMARY

Sixteen gametocyte carriers treated with daraclor syrup were all free of gametocytes 35 days after treatment. Neither chloroquine nor pyrimethamine is supposed to be a gametocide. It is possible that the syrup suspension is a significantly more effective medium of treatment than tablets.

Transmission experiments will have to be made to determine whether a sporontocidal action was effective during the days that gametocytes were present in the blood after treatment.

The syrup tried was sufficiently acceptable to small children and, as far as this trial shows, it is undoubtedly the treatment of choice for children up to the age of 12 years.

The advantages of a suspension over tablets are so great that research chemists should make further efforts to produce a suspension sufficiently concentrated for adult use.

Further investigations are required to determine the sporontocidal action of the syrup, the subjective results of curing 'symptomless carriers', and the practicability of using a 'temperature index' for selecting cases for blood examination. It is likely that temperature recording will produce better results than spleen palpation—it is certainly easier to teach to field workers.

In any investigations undertaken, accurate records must be kept of symptomless carriers for at least 10 days and those should include temperature charts, spleen rates, an assessment of physical and mental health and efficiency, subjective symptoms, and effects of treatment.

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APPENDIX

Thin and thick blood smears were taken of each patient before admission, and daily after treatment for 7 days. At least 100 microscopic fields were examined before admission, to determine the density of parasites. No parasite count was made, but the following terms were used to indicate the density of parasites:

Heavy (+++): Heavy infections. Ring forms and gametocytes abundant.

Medium (++) : Moderate infections. Ring forms and gametocytes not so plentiful.

Low (+) : Low infections. Ring forms and gametocytes very scanty.

In cases where no ring forms or gametocytes could be found, the smears were examined by four other microscopists to eliminate the possibility that rings or gametocytes were missed or overlooked.

Disintegrated gametocytes were found only in smears after treatment.

In some cases gametocytes appeared in blood smears after treatment. Blood smears of such persons were re-examined.

In all cases (except one) in which disintegrated gametocytes were found, the normal gametocytes were predominant.