

Trials of Proguanil Hydrochloride on Ceylon Estates

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(A) Single Dose Therapy for Attacks of Malaria :—

Outpatient treatment of malaria is common in Ceylon, and as the average estate labourer generally refuses to attend further at the dispensary once the acute symptoms of his attack have subsided, it is inevitable that a large percentage of cases receive only one day's treatment. These practices have given the patients every opportunity of developing premunity to the local strains of parasites.

With the introduction of proguanil hydrochloride single dose therapy was advocated, particularly for such persons. The administrative advantages of this type of therapy are obvious, but it seemed necessary to determine its effectiveness in an attack of malaria, and its influence, if any, on the relapse rate, under the prevailing conditions here, before advocating it as a routine. With this object in view, two tea estates located in the more malarious dry zone were chosen, and a trial started in July, 1947, with the malaria cases as they appeared.

Cases :—By the beginning of 1947 larvae control methods had been abandoned and were replaced by residual spraying of habitations with D.D.T. It is well known that this change in the anti-malaria measures has produced a dramatic reduction in the malaria incidence in Ceylon. Its relevancy to this article lies in the fact that, from a combined population of 5,280 for the two estates plus an unknown number of villagers, we managed to secure only 88 blood positive cases of malaria during the 25 months of the trial. Of these, 19 could not be traced later, one was a case of cerebral malaria in a child, and two other cases had to receive more than a single dose of proguanil. This reduced the total cases in this series to 66. Though few, they constitute a fair sample under present conditions, and merit report, because of the period of observation to which they have been subjected, and because they refer to Ceylon strains.

The species of plasmodium present in the 66 cases of this series were distributed as follows :— *Plasmodium falciparum* 26 cases ; *Plasmodium vivax* 26 cases ; *Plasmodium malariae* 8 cases ; and mixed *P. falciparum* and *P. vivax* 6 cases ; Total 66 cases.

Most of the cases had some premunity, and 78% showed some enlargement of the spleen on admission for the initial attack. The details of the splenic enlargement found are given in Table No. 1.

TABLE No. 1
Details of Cases with Enlarged Spleens on Admission

Species of Parasite Present	Number of cases showing Splenic Enlargement on Admission			Total Cases
	Negative	± *	+ †	
<i>P. falciparum</i>	5	20	1	26
<i>P. vivax</i>	6	17	3	26
<i>P. malariae</i>	3	5	-	8
Mixed <i>P. falciparum</i> and <i>P. vivax</i>	Nil	4	2	6
Total	14	46	6	66

± * = Spleen that extended to the costal margin.

+ † = Spleen extending into the first third of the distance from the costal margin to the umbilicus.

Technique Employed :—Most of the cases of malaria were admitted to the estate hospital, but some had to be treated as outpatients. Thick blood films were taken daily for the first 5 days; and only those with positive blood slides were included in the trial. Each film was searched completely before being pronounced negative. In positive cases the number of parasites present in 50 consecutive microscopic fields were counted; the average per field ascertained; and this average is used below for denoting the degree of infection.

Treatment consisted in the administration of a single dose of proguanil hydrochloride on the day of admission, the dosage being 300 mg. for those 15 years and over, and 200 mg. for those aged 2 years to 14 years. Relapses were treated similarly to initial attacks.

Treatment of cases commenced in July 1947, and ceased in August 1949. All cases reported have been followed up till March 1950.

Results :—In two instances the single dose failed to control the pyrexia. One was a case of *Plasmodium vivax* infection in a boy aged 12 years, who had, on admission, a temperature of 102°F; an average of 1·8 asexual parasites per field; and a + spleen. On this day he received 200 mg. of proguanil hydrochloride; on the following day his temperature was normal; and the asexual parasites had fallen to an average of 0·8 per field; on the second day after admission his temperature rose to 105°F and as he was in obvious distress the dose of proguanil was repeated, but the blood film, which was examined later, proved negative. He remained free from fever for the next 73 days, at which stage his blood film showed an average of 2·4 asexual parasites per field. His spleen, though still enlarged, had decreased to ± in size. He was given a single dose of proguanil hydrochloride (200 mg.), and has remained free from fever for the past 18 months. As he had two doses of proguanil in his initial attack he has not been included in the series.

The second case was a woman in whom the single dose of proguanil (300 mg.) had successfully controlled the pyrexia and rendered her blood slides negative within 24 hours of her initial attack of quartan. She relapsed on the 84th day, with a

temperature of 102°F, and an average of 0.6 asexual quartan parasites per field. She was given a single dose of 300 mg. proguanil, and the parasites decreased daily in number till they disappeared from the films on the fourth day of the relapse. She continued, however, to have the classical quartan temperature and on the third rise (i.e. on the 10th day of the relapse) after the exhibition of the drug reached 103°F. At this stage she was given 300 mg. proguanil daily for 6 days. This controlled the fever but 47 days after the completion of this course she suffered a clinical relapse, with a temperature of 100°F but negative blood films. The 6-day course was repeated and she has remained well during the past 220 days.

In one initial attack of quartan, though the pyrexia disappeared within 24 hours, it was not till the 7th day that the blood films were free of asexual parasites. The remainder, consisting of 65 initial attacks and 29 relapses, were freed of fever and had blood films negative for asexual parasites, within 4 days.

Pyrexia :—The details of the effect of the single dose of proguanil hydrochloride on the pyrexia of the initial attacks are given in Tables Nos. 2 and 3.

TABLE No. 2

Number of Cases freed of Pyrexia during the first four days following the Exhibition of a single dose of Proguanil Hydrochloride

Species of Parasites	Number of Cases	Average Maximum Temperature on day of Admission	Number of Cases free from Pyrexia within			
			24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.
<i>P. falciparum</i>	26	101.7	13	18	24	26
<i>P. vivax</i>	26	101.3	14	19	25	26
<i>P. malariae</i>	8	101.0	7	8	8	8
Mixed MT and BT	6	103.0	4	5	6	6
All Species	66	101.6	38	50	63	66

TABLE No. 3

Average maximum temperatures during the first four days

Species of Plasmodia	D Day			D + 1			D + 2			D + 3			D + 4
	Max	Min	Av.	Max	Min	Av.	Max	Min	Av.	Max	Min	Av.	
MT	104	100	102	103	99	101.4	102	99	100.1			99	All normal
BT	104	99	101.3	102	99	100.6	103	99	100.6			100*	
Q	103	100	101.0			100*	All normal			All normal			
Mixed MT & BT	105	101	103.0	104	99	101.5	102	101	101.5	All normal			
All Species	105	99	100.6	104	99	100.9	103	99	100.5			99.3	

*1 case only in each instance.

Parasitaemia :—The effect of the single dose on the asexual parasites in the daily thick blood films is given in Tables Nos. 4 and 5.

TABLE No. 4
Periods required to render thick films negative for asexual parasites

Species of Parasite	No. of Cases	Average Number of Asexual Parasites per Field* on Admission	Number of Cases with Negative Blood films within			
			24 Hrs.	48 Hrs.	72 Hrs.	96 Hrs.
<i>P. falciparum</i>	26	7.9	11	18	20	26
<i>P. vivax</i>	26	7.0	13	17	26	26
<i>P. malariae</i>	8	1.0	6	7	7	7†
Mixed <i>P. falciparum</i> & <i>P. vivax</i>	6	3.9	2	4	6	6
All Species	66	6.1	32	46	59	65

*Average parasites per field of 50 consecutive fields.

†One case remained positive till the 7th day.

TABLE No. 5
Average number of asexual parasites per field of 50 consecutive fields in cases with positive films

Species of Parasite	D Day			D + 1			D + 2			D + 3		
	Max	Min	Av.	Max	Min	Av.	Max	Min	Av.	Max	Min	Av.
<i>P. falciparum</i>	38.6	0.2	7.9	16.8	0.2	2.2	0.4	0.13	0.2			0.3*
<i>P. vivax</i>	47.8	0.4	7.0	13.4	0.6	3.6	7.6	2.2	3.3	All negative		
<i>P. malariae</i>	2.2	0.3	1.0	1.0	0.6	0.8			0.6*			0.6*
Mixed BT & MT	9.0	1.6	3.0	6.2	0.4	3.4			3.4	All negative		
All Species	47.8	0.2	6.1	16.8	0.2	2.7	7.6	0.13	1.6			

* 1 case only in each instance.

All cases had negative films by D + 4 except one case of quartan which became negative on D + 7.

Relapses :—The term 'relapse' is undoubtedly used in its correct sense in these cases, but some of the initial attacks were probably relapses. This, combined with the premunity present in many cases would seem to account for the comparatively low relapse rates.

Table No. 6 gives the number of relapses that occurred with each species of plasmodium present.

TABLE No. 6
Number of Cases which Relapsed

Cases Treated		Relapses		
Type	Number	First	Second	Third
M.T.	26	3	—	—
B.T.	26	9	3	—
Quartan	8	3	1	—*
Mixed M.T. & B.T.	6	5	3	2
Total	66	20	7	2
Percentage		30.6%	10.6%	3.0%

*The case of quartan had a possible third relapse, with the clinical symptoms but the blood films were negative.

The minimum periods of observation since the last relapses were 15 months in the M.T. cases, 7 months in the B.T. cases, 10½ months in the Quartan cases, and 14 months in the mixed M.T. and B.T. cases.

A large series of cases were treated with a single dose of 300 mg. paludrine, in different parts of India, by a number of workers in conjunction with Afridi (1947). Of these cases, within 3 days, 93% were free of fever, and 72% had blood films free of asexual parasites. The readmission rate did not exceed 25%. As a result of this investigation Afridi recommended this single dose as the most desirable course, both for hospitals and dispensaries in India.

In our series, within 72 hours of admission, 95.4% of cases were free of pyrexia, and 89.4% of the blood films were negative for asexual parasites. The relapses, however, were more numerous, for 30.6% relapsed once, 10.6% relapsed twice, and 3.0% relapsed thrice, the blood films being positive in each case. There were in all 29 readmissions among 66 original cases, and this would amount to a readmission rate of 43.9%. In addition to the case of cerebral malaria, two others had to receive more than a single dose.

Though the repetition of the dose in only 2 out of 99 initial and subsequent attacks presents no difficulty, and in both cases was effective, this factor has to be considered in conjunction with the others which form the complete picture of malaria in Ceylon. Here the marked success of residual insecticide spraying has reduced the chances of reinfection far below that general in many parts of India. As a result of this, the percentage of the population possessing resistance to malaria is diminishing rapidly each year, and, concomitantly, increasing readmission rates may be expected to follow single dose therapy. Under these circumstances it would seem wisest to aim at radical cure wherever possible, and for this purpose full courses of proguanil are indicated.

(B) Effect of Proguanil on Enlarged Spleens in Children:—

Technique Employed:—Incidental to a trial of weekly doses of proguanil as a suppressive, commenced on another estate in July, 1946, the spleen rates of the children were ascertained.

The children aged 2 to 10 years were divided into two groups of 45 each and equal in distribution in respect of sex, age, and site of residence. The spleen rates in both groups were ascertained on the 16th July, and again on the 26th October. To one group proguanil hydrochloride was administered once a week, while the other group was used as a control. By the time of the second spleen examination the numbers had decreased to 40 in the proguanil group and 29 in the control group, and only these numbers are included in the results. The examiner had no idea as to which group the children belonged when he examined them for splenic enlargement.

The following terms are used to describe the various degrees of splenic enlargement encountered:—Negative:—a spleen that was unpalpable. Plus/minus:—a spleen that could be palpated but could be pushed up behind the costal margin. The region between the costal margin and the umbilicus was then divided into three equal parts, and spleens whose lower poles were in the first part (i.e. the part nearest to the costal margin) but could not be pushed up behind the costal margin were designated plus one; those in the second part were called plus two; and those in the third part were described as plus three. No spleens extending beyond the umbilicus were encountered at either muster.

The amount of proguanil hydrochloride exhibited to the trial group of children was 50 mg. once a week for 14 occasions between the first and second spleen musters.

Parasite Rates:—The parasite rate was 23·3% in the proguanil group and 31·3% in the control group on the 16th July. On the 26th October the parasite rates were nil in the proguanil group and 18·8% in the control group.

Reduction in Spleen Rate:—The spleen rate which was 41·4% in the control group at the first muster fell to 37·9% at the second muster, 14 weeks later. In the proguanil group, on the other hand, a spleen rate of 47·5% at the first muster decreased to 20% at the second muster. This is a purely quantitative statement. Table No. 7 shows the diminution in size of the spleens in the two groups:—

TABLE No. 7

Number Examined		Proguanil Group		Control Group	
		40		29	
Date		16th July	26th Oct.	16th July	26th Oct.
Size of Spleen.	Neg.	21	32	17	18
	±	12	8	3	3
	+	2	—	3	3
	++	3	—	1	3
	+++	2	—	5	2
Percentage Positive		47·5%	20%	41·4%	37·9%

From Table No. 7 it will be seen that, in the proguanil group, not only was the spleen rate more than halved, but also that no spleen larger than ± remained. Compared with the results obtained from the stock spleen mixtures used on estates before the war, this effect of 14 weekly doses of proguanil was a very big improvement.

Summary

Of 69 blood positive malaria cases which could be followed up, one suffered from cerebral malaria, while one initial attack of benign tertian and one relapse of quartan had to have more than a single dose of 300 mg. of proguanil hydrochloride to render them free of pyrexia.

The remaining 66 cases consisted of:—subtertian 26 cases, benign tertian 26 cases, quartan 8 cases, and mixed subtertian and benign tertian 6 cases.

Of these 66, a single dose of proguanil hydrochloride (200 mg. for those under 15 years of age, and 300 mg. for those 15 years and over) eliminated the pyrexia in 57.6% of cases within 24 hours; in 75.8% of cases within 48 hours; in 95.4% of cases within 72 hours; and in 100% within 96 hours.

In these 66 cases, the same single dose caused the asexual parasites to disappear from thick blood films in 48.5% of cases within 24 hours; in 69.7% within 48 hours; in 89.4% of cases within 72 hours. On the 4th day only one case of quartan had positive slides which, in the absence of further treatment, became negative on the 7th day.

With the exception of one case which required a second dose of proguanil, the B.T. cases clinically responded slightly better than the M.T. cases. The quartan cases responded best of the three, but the numbers are too few for definite conclusions to be drawn.

Of the 66 cases, 30.6% relapsed once; 10.6% relapsed twice; and 3.0% relapsed thrice, the total readmission rate being 43.9%. The M.T. cases had the fewest relapses and the mixed infections of M.T. and B.T. the most. The minimum period of observation from the last attack was 7 months in one case of B.T. and over 10 months in all other cases.

The present high standard of malaria control in Ceylon renders the chances of re-infection small, and concomitantly lowers the resistance of the population to this disease. Treatment should, therefore, aim at eradication of the parasites from the patients, and for this single dose therapy is not recommended.

Among children aged 2 to 10 years 14 weekly doses of 50 milligrammes of proguanil hydrochloride more than halved the spleen rate, and in all the cases which were still enlarged the spleen had receded to the costal margin.

References

AFRIDI, M. K. (1947). *Indian Journal of Malariology*, Vol. I, No. 3.