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THE SINGLE DOSE TREATMENT OF HUMAN MALARIA BY DIAMINO-DIPHENYL-SULFONE (DDS), SINGLY AND IN COMBINATION WITH PYRIMETHAMINE. A PRELIMINARY STUDY OF THEIR EFFECTS IN P. VIVAX AND P. FALCIPARUM INFECTIONS IN RAJASTHAN, INDIA[1]

by

P. C. Basu, M. M. Mondal & S. C. Chakrabarti
(Malaria Institute of India, Delhi, India)

Diamino-diphenyl-sulfone (DDS) has been shown to cause quick selection of resistance in P. cynomolgi. It has been further demonstrated that the DDS-resistant parasites while equally resistant to sulfadiazine did not show any cross resistance to pyrimethamine (Ramakrishnan, Basu et al. 1961). This finding was of considerable importance in favour of the combined use of these two drugs. Laboratory studies were commenced to investigate actual potentiation, if any, of DDS and pyrimethamine.

In the meantime, advantage was taken of a focal outbreak of malaria amongst the inhabitants of Jodhpur and of its environs (Rajasthan State) to investigate the role of DDS singly and with pyrimethamine in the treatment of human malaria. The investigation was based in the Sursagar Government Dispensary situated at the outskirts of Jodhpur City. The results of the preliminary trial carried out in October 1961 are set out in this paper. The outbreak in this locality was due to an operational failure of the DDT spraying under the National Malaria Eradication Programme.

Methods

All fever cases reporting to the dispensary were examined microscopically. Only cases found positive for malaria parasites were treated according to one or other of the regimens detailed below. The treatment was ambulatory and in no case was hospitilization necessary.

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[1] Research project carried out by the Malaria Institute of India with the partial financial assistance of the World Health Organization.

The drug was administered in one single dose by mouth under strict supervision. DDS[1] tablets containing 100 mg each and pyrimethamine[2] tablets containing 25 mg each were used in this investigation. Proportionate fractional dosages (Table 1) of the tablets were carefully ensured by the authors before actual administration.

Five drug regimens were used. The smaller dosages of DDS were deliberately chosen for the purpose of potentiation, if any, between this drug and pyrimethamine. The details of the regimen and the proportionate age-group dosage are shown in Table 1.

TABLE 1. SINGLE DOSE REGIMENS FOR ADULTS AND PROPORTIONATE DOSAGE FOR DIFFERENT AGE-GROUPS. (Doses for age-groups not available for treatment in the different regimens are omitted)

Age-group	Regimen (dosage in mg)							
	I	II	III		IV		V	
	DDS only	DDS only	DDS + pyrimethamine		DDS + pyrimethamine		DDS + pyrimethamine	
A Adults	250	200	100	12.5	50	12.5	25	12.5
B 9-14 yrs	175	150	-	-	33.0	8.3	16.6	8.3
C 5-8 yrs	-	100	-	-	25.0	6.0	12.5	6.0
D 1-4 yrs	75	50	-	-	12.5	3.0	6.2	3.0
E Infants	-	-	-	-	6.2	1.6	-	-

[1] "Avlosulfon" (Dapsone) Tablets B.P. 0.1 g. Imperial Chemical Industries (India) Private Ltd., Calcutta. (prop. I.N.N. = diaphenylsulfone)

[2] "Daraprim" brand pyrimethamine B.P.C. Tablets. 25 mgm. Burroughs Wellcome & Co. (India) Private Ltd., Bombay.

The cases were classified into five age-groups - A to E (Table 2). All cases had fever when they were first seen. Parasitaemia was investigated by the use of both thick and thin blood smears. The degree of parasitaemia was ascertained by counting the number of parasitized cells per 10 000 erythrocytes. Asexual parasite density index was calculated as described by Bruce-Chwatt (1951, 1958) and daily on the subsequent days of the observation period. The total erythrocyte count was, however, not determined and was assumed to be five million per cmm in each case.

TABLE 2. DETAILS OF AGE, INFECTION, PARASITE DENSITY INDEX AND PYREXIA IN RESPECT OF THE FIVE GROUPS OF SUBJECTS BEFORE TREATMENT

	Age-group				
	A (15 yrs and above)	B (9-14 yrs)	C (5-8 yrs)	D (1-4 yrs)	E (Infants)
Number (Male	21	10	6	5	1
Number (Female	8	2	2	3	1
Number (Total	29	12	8	8	2
Age in years (Mean	27.9	12.1	5.8	2.7	0.7
Age in years (Range	15-65	10-14	5-8	1-1/2-4	5/12-1
Parasite species and number of cases	P.v. 14 P.f. 12 P.v. + P.f. 3	P.v. 7 P.f. 5	P.v. 5 P.f. 2 P.v. + P.f. (mixed) 1	P.v. 6 P.v. + P.f. (mixed) 2	P.v. 2
Parasite density index	5.8	7.2	6.2	7.1	8.5

P.v. = Plasmodium vivax

P.f. = Plasmodium falciparum

No case selection was made regarding the adoption of a particular regimen. The cases were treated in serial order as they became available, the first one with regimen I, the second with regimen II and so on till the sixth case was treated with regimen I again and the same serial order was followed.

Due to the past endemicity of malaria in the area, it appeared that the different age-groups varied in the degree of acquired immunity to the infection. The infants had little or no immunity while the immunity was gradually higher in each older group; this difference in the immune status was reflected in the initial parasite density indices (Table 2).

Each treated case was observed for five days following treatment by daily clinical and parasitological examination which involved visits to the patients' homes or places of work. The cases which were cleared of asexual parasites by the regimens under investigation were transferred to the National Malaria Eradication Programme surveillance organization for radical treatment with primaquine after the expiry of five-day observation. Cases which were not cleared of asexual parasites by the fifth day of the trial dose or sometimes earlier, received the standard single dose treatment with chloroquine and were also transferred to surveillance organization.

Results

The results have been analysed for each regimen with respect to the following criteria:

(a) parasite density index (PDI), its initial value and the trend of its decline;

(b) initial fever and its termination;

(c) response of the two species of parasites (*P. falciparum* and *P. vivax*);

(d) clearance time of asexual parasites; and

(e) effect on gametocytes in the peripheral blood.

The determination of the relapse pattern after treatment by the different regimens did not arise as radical treatment with primaquine of every positive case was obligatory.

Only one case of vomiting was noted in a male aged 20 years treated under regimen II (sulfone 200 mg - single adult dose). The vomiting occurred 24 hours after drug administration and required no further palliative treatment. No skin rash was encountered. No toxic symptoms were noted either subjective or objective unequivocally attributable to any of these regimens of treatment.

Tables 3, 4 and 5 show the results of treatment by regimen I.

1. P. vivax

Pyrexia was cleared in all the seven cases within 72 hours. Asexual parasites were cleared within 72 hours of drug administration in five out of seven cases (Table 3). The two cases in which the asexual parasites were not cleared belonged to the age-group D. The parasitaemia in one of the cases (1-1/2 years old) showed progressive decrease though the asexual parasites persisted even up to 96 hours of drug administration; in the other (four years old) the parasitaemia fell within 48 hours and was followed by a gradual increase which persisted up to 96 hours. Both these cases received a further single dose treatment with chloroquine. The asexual parasite density index decreased from 5.4 on D day to 1.8 on D + 4 day (Table 4). Gametocytes were not cleared in two out of the four cases in which these were detected within 48-72 hours of drug administration (Table 5).

2. P. falciparum

Pyrexia was cleared in all the four cases within 72 hours. Asexual parasites were cleared in all the cases within 72 hours of drug administration (Table 3). The parasite density index dropped from 5.0 on D day to 0 on D + 3 day (Table 4). Gametocytes were not detected in any of the four cases during the period of observation (Table 5).

3. Mixed infection

One case (three years old) of mixed infection became afebrile within 24 hours. Asexual parasites of P. falciparum were cleared within 24 hours of drug administration while those of P. vivax persisted up to 120 hours (Table 3). The asexual parasite density index declined from 7 to 5 on D + 1 day but again P. vivax increased to 6 on D + 4 day (Table 4). Gametocytes of both the species persisted in the circulation (Table 5).

TABLE 3. EFFECT OF A SINGLE DOSE OF 250 MG DDS ON THE CLEARANCE OF ASEXUAL PARASITES (REGIMEN I)

Age-group	*P. vivax* infection clearance within hours						*P. falciparum* infection clearance within hours						*P. vivax* and *P. falciparum* (mixed) infection clearance within hours	
	No. of cases	24	48	72	96	Not cleared	No. of cases	24	48	72	96	Not cleared	No. of cases	
A Adults	3		2	1			3		2	1		Nil		
B (9-14 yrs)	1			1			1	1				Nil		
D (1-4 yrs)	3		1			2							1	One case aged 3 years. *P. falciparum* asexual parasites cleared within 24 hours. *P. vivax* asexual forms not cleared within 120 hours.
Total	7		3	2		2	4	1	2	1		Nil	1	

TABLE 4. ASEXUAL PARASITE DENSITY INDEX (REGIMEN I)

	P. vivax	P. falciparum	P. vivax and P. falciparum
On D day	5.4	5.0	7.0
On D + 1 day	4.2	2.2	5.0
On D + 2 day	1.7	1.2	5.0
On D + 3 day	1.5	0	5.0
On D + 4 day	1.8	0	6.0
On D + 5 day	Not recorded	0	Not recorded

Regimen I was effective in controlling the fever in all cases of P. vivax infection but proved ineffective in securing complete disappearance of asexual parasites in three children. Against P. falciparum, the regimen was effective in clearing the parasites as well as fever within 72 hours. The case of mixed infection demonstrated that P. falciparum was more sensitive to DDS than P. vivax.

Tables 6, 7 and 8 show the results of treatment by regimen II.

1. P. vivax

All the seven cases became afebrile within 72 hours. Asexual parasites were cleared within 96 hours in five cases while in the other two cases (one adult and one child aged two years) they continued to be patent up to 120 hours of drug administration (Table 6). The asexual parasite density index declined from 7.3 on D day to 1.0 on D + 5 day (Table 7). Gametocytes were detected in three cases only and these continued to be observed up to five days after drug administration in two, while in one, the gametocytes disappeared within 72 hours (Table 8).

TABLE 5. EFFECT ON GAMETOCYTES (REGIMEN I)

Type of infection	No. of cases	Gametocytes absent initially	Appearance within hours of drug administration						Clearance within hours of drug administration			Total not cleared
			24	48	72	96	120	Total	72	96	120	
P. vivax	7	7	-	2	2	-	-	4	1	1	-	2
P. falciparum	4	4	-					Nil				
Mixed P.v./P.f.	1	1	-	0/1	1/1			1/1				1/1

TABLE 6. EFFECT OF A SINGLE DOSE OF 200 MG DDS ON THE CLEARANCE OF ASEXUAL PARASITES (REGIMEN II)

Age-group	*P. vivax* infection clearance within hours							*P. falciparum* infection clearance within hours				*P. vivax* and *P. falciparum* (mixed) infection clearance within hours	
	No. of cases	24	48	72	96	120	Not cleared	No. of cases	24	48	Not cleared	No. of cases	
A Adults	3	2					1	1	1		Nil	1	P.v. asexual form not cleared within 120 hours. P.f. asexual form cleared within 72 hours
B (9-14 yrs)	1	-	-	1			Nil						
C (5-8 yrs)	2	1			1		Nil	2	1	1	Nil	1	P.v. asexual form cleared within 72 hours. P.f. asexual form cleared within 48 hours
D (1-4 yrs)	1	-	-	-	-		1						
Total	7	3		1	1		2	3	2	1	Nil	2	

P.v. = *Plasmodium vivax*

P.f. = *Plasmodium falciparum*

TABLE 7. ASEXUAL PARASITE DENSITY INDEX (REGIMEN II)

	P. vivax	P. falciparum	P. vivax and P. falciparum
On D day	7.3	4.0	5.0
On D + 1 day	3.5	1.0	4.0
On D + 2 day	1.5	0	3.0
On D + 3 day	1.4	0	2.5
On D + 4 day	1.0	0	1.5
On D + 5 day	1.0	0	2.5

2. P. falciparum

The fever as well as the asexual parasites disappeared in all the three cases within 48 hours of drug administration (Table 6). The parasite density index dropped to zero from the initial value of 4.0 within 48 hours (Table 7). The gametocytes were not cleared within the period of observation in the two cases in whom such forms appeared (Table 8).

3. Mixed infection

Both cases became afebrile within 72 hours. In one, the asexual forms of both the species were cleared within 48 to 72 hours. In the other case (adult, aged 28 years) the asexual stages of P. falciparum were cleared within 72 hours but the corresponding stages of vivax persisted up to 120 hours (Table 6). The asexual parasite density index declined from the initial 5.0 to 1.5 within 96 hours of treatment but thereafter (P. vivax) registered a rise to 2.5 (Table 7). Gametocytes of both species were not cleared (Table 8).

Regimen II was ineffective in two out of seven cases of P. vivax infection although one of the subjects (28 years) treated was semi-immune. The time taken for clearance of asexual forms in the other five cases was longer than under

TABLE 8. EFFECT ON GAMETOCYTES (REGIMEN II)

Type of infection	No. of cases	Gametocytes absent initially	Appearance within hours of drug administration						Clearance within hours of drug administration					Total not cleared
			24	48	72	96	120	Total	24	48	72	96	120	
P. vivax	7	6	2	-	-	-	-	3			1			2
P. falciparum	3	3	2	-	-	-	-	2	-	-	-	-	-	2
P.v./P.f.	2	2	-	2 (0/1 and 1/0)	-	-	-	2	-	-	-	-	-	1/1

TABLE 9. EFFECT OF A SINGLE DOSE OF 100 MG DDS COMBINED WITH 12.5 MG OF PYRIMETHAMINE ON THE CLEARANCE OF ASEXUAL PARASITES (REGIMEN III)

Age-group	*P. vivax* infection clearance within hours							*P. falciparum* infection clearance within hours						
	No. of cases	24	48	72	96	120	Not cleared	No. of cases	24	48	72	96	120	Not cleared
Adults	6	2	3	1	-	-	Nil	6	4	2	-	-	-	Nil
Total	6	2	3	1	-	-	Nil	6	4	2	-	-	-	Nil

TABLE 10. ASEXUAL PARASITE DENSITY INDEX (REGIMEN III)

	P. vivax	P. falciparum
On D day	6.8	3.0
On D + 1 day	4.1	1.6
On D + 2 day	0.5	0
On D + 3 day	0	0
On D + 4 day	0	0
On D + 5 day	0	0

regimen I. Against P. falciparum infection the regimen was found quite effective both in respect of fever and asexual parasites but in one case of mixed infection it failed to clear the asexual forms of P. vivax. Like regimen I, this also proved to be inadequate for the treatment of vivax malaria since the asexual parasites persisted in three out of nine cases.

Tables 9, 10 and 11 show the results of treatment by regimen III.

1. P. vivax

All the six patients were free from pyrexia within 48 hours and asexual parasites were cleared within 72 hours (Table 9). Asexual parasite density index showed a drop from 6.8 to zero within 72 hours (Table 10). Five cases had shown gametocytes either initially or following the treatment. The gametocytes were cleared in four cases within 72 hours but in one they persisted up to at least 120 hours (Table 11).

2. P. falciparum

Fever and asexual parasitaemia were cleared within 48 hours in all the six cases (Table 9). Asexual parasite density index was reduced to zero within 48 hours from the initial value of 3.0 (Table 10). Crescents, observed initially in three cases, failed to clear up within 120 hours of the treatment (Table 11).

TABLE 11. EFFECT ON GAMETOCYTES (REGIMEN III)

Type of infection	No. of cases	Gametocytes absent initially	Appearance within hours of drug administration					Clearance within hours of drug administration					Total not cleared
			24	48	72	96	120	Total	24	48	72	96	120	
P. vivax	6	3	2	-	-	-	-	5	1	2	1	-	-	1
P. falci-parum	6	3	-	-	-	-	-	3	-	-	-	-	-	3

Under this combined regimen in all the 12 cases clearance of asexual parasites as well as disappearance of fever was noted within 48 to 72 hours. The clearance of P. vivax gametocytes appeared to be better than that observed under regimens I and II. The gametocytes of P. falciparum, however, persisted during the period of observation.

Tables 12 to 14 show the results of treatment by regimen IV.

1. P. vivax

The fever disappeared in all the 10 cases within 48 hours; asexual parasites were cleared in all of them within 72 hours. The asexual parasite density index declined from the initial 7.4 to zero within 72 hours (Tables 12 and 13). Gametocytes were detected in nine out of 10 cases and only in two they persisted at least up to 120 hours of drug administration (Table 14).

2. P. falciparum

All the five cases were rendered free from fever as well as asexual parasites within 72 hours of drug administration. The asexual parasite density index was reduced to zero from the initial 7.6 within 72 hours (Tables 12 and 13). Crescents were observed in four cases and they continued to be present in two cases up to at least 120 hours of the drug administration (Table 14).

3. Mixed infection

Two cases which showed mixed infection were cleared within 48 to 72 hours of fever as well as of asexual parasites of both species. The asexual parasite density index was reduced to zero from the initial 9.0 within 72 hours of the treatment (Tables 12 and 13). Gametocytes continued to be present up to 120 hours of drug administration in both the cases; this involved both species in one case and crescents only in the other (Table 14).

The cases treated under this regimen represented all age-groups; the infants with a low degree of immunity and the semi-immune adults. All the 17 cases were rendered afebrile within 72 hours irrespective of the type of infection. Similarly clearance of the asexual parasites of both species was secured in all the 17 cases within 72 hours of the drug administration.

TABLE 12. EFFECT OF A SINGLE DOSE OF 50 MG DDS COMBINED WITH 12.5 MG OF PYRIMETHAMINE ON CLEARANCE OF ASEXUAL PARASITES (REGIMEN IV)

Age-group	P. vivax infection clearance within hours					P. falciparum infection clearance within hours					P. vivax and P. falciparum (mixed) infection clearance within hours	
	No. of cases	24	48	72	Not cleared	No. of cases	24	48	72	Not cleared	No. of cases	
A Adults	1	1			Nil	3	1	1	1	Nil	1	P.v. asexual forms cleared within 72 hours. P.f. asexual forms cleared within 72 hours.
B (9-14 yrs)	4	1	1	2	Nil	2	-	2		Nil		
C (5-8 yrs)	2	2			Nil							
D (1-4 yrs)	1	-	1		Nil						1	P.v. asexual forms cleared within 72 hours. P.f. asexual forms cleared within 48 hours.
E (Infants)	2	-	2		Nil							
Total	10	4	4	2	Nil	5	1	3	1	Nil	2	

TABLE 13. ASEXUAL PARASITE DENSITY INDEX (REGIMEN IV)

	P. vivax	P. falciparum	P. vivax and P. falciparum
On D day	7.4	7.6	9.0
On D + 1 day	3.9	5.0	9.0
On D + 2 day	1.3	1.0	8.0
On D + 3 day	0	0	0
On D + 4 day	0	0	0
On D + 5 day	0	0	0

The gametocytes of P. vivax were cleared in eight out of 11 cases which showed these forms. Crescents appeared to remain unaffected.

Tables 15, 16 and 17 show the results of treatment by regimen V.

1. P. vivax

The pyrexia disappeared in all the four cases within 72 hours. Two were cleared of asexual parasites only on the D + 5 day, whereas the other two continued to show the asexual parasites throughout the period of observation (Table 15). Asexual parasite density index declined from 6.7 on D day to 2.0 on D + 4 day but again rose to 2.5 on D + 5 day (Table 16). Gametocytes observed in four cases continued to be present during the period of observation (Table 17).

2. P. falciparum

Only one case (aged 10 years) was treated under this regimen. The fever remained high and the asexual parasites persisted up to 72 hours of the drug administration necessitating treatment with chloroquine. The asexual parasite density index during the period of observation declined from 9.0 on D day to 0.8 on D + 3 day (Tables 15 and 16). Gametocytes were not detected in this case.

TABLE 14. EFFECT ON GAMETOCYTES (REGIMEN IV)

Type of infection	No. of cases	Gametocytes absent initially	Appearance within hours of drug administration						Clearance within hours of drug administration					Total not cleared
			24	48	72	96	120	Total	24	48	72	96	120	
P. vivax	10	2	1	-	-			9	3	2	1		1	2
P. falciparum	5	4	2	1				4	1		1			2
Mixed P.v./P.f.	2	2	1/1 1/0	1/1				2	-	-	-	-	0/1	2

TABLE 15. EFFECT OF A SINGLE DOSE OF 25 MG DDS COMBINED WITH 12.5 MG OF PYRIMETHAMINE ON THE CLEARANCE OF ASEXUAL PARASITES (REGIMEN V)

Age-group	*P. vivax* infection clearance within hours							*P. falciparum* infection clearance within hours					*P. vivax* and *P. falciparum* (mixed) infection clearance within hours	
	No. of cases	24	48	72	96	120	Not cleared	No. of cases	24	48	72	Not cleared	No. of cases	
A Adults	1					1							1	P.v. asexual forms cleared within 96 hours. P.f. asexual forms cleared within 72 hours.
B (9-14 yrs)	1						1	1*				1		
C (5-8 yrs)	1						1							
D (1-4 yrs)	1					1								
Total	4					2	2	1				1	1	

* The case was observed up to 72 hours, the fever did not come down and the parasite count was also high; he was given chloroquine treatment at the end of this period.

TABLE 16. ASEXUAL PARASITE DENSITY INDEX (REGIMEN V)

	P. vivax	P. falciparum	P. vivax and P. falciparum
On D day	6.7	9.0	7.0
On D + 1 day	6.0	8.0	5.0
On D + 2 day	4.7	8.0	5.0
On D + 3 day	5.0	0.8	5.0
On D + 4 day	2.0	Not observed	0
On D + 5 day	2.5	Not observed	0

3. Mixed infection

One case of mixed infection treated under this regimen was rendered afebrile within 48 hours and showed clearance of asexual parasites (both species) within 72-96 hours. The asexual parasite density index was reduced from the D day value of 7.0 to zero within 96 hours. The P. vivax gametocytes were not cleared within the period of observation (Tables 15 to 17).

A total of six cases were treated under regimen V. With regard to the clearance of asexual parasites this regimen proved ineffective in three cases with either P. vivax or P. falciparum infections. In one case the fever persisted in spite of the treatment and recourse had to be taken to an alternate drug. The time taken for the clearance of asexual forms of P. vivax was long (120 hours). The gametocytes of P. vivax remained apparently unaffected by this regimen.

Discussion

A single dose of 250 or 200 mg of DDS was invariably effective in all the P. falciparum infections but proved ineffective in clearing the asexual parasites in six out of 17 P. vivax infections (Tables 3 and 6).

TABLE 17. EFFECT ON GAMETOCYTES (REGIMEN V)

Type of infection	No. of cases	Gametocytes absent initially	Appearance within hours of drug administration						Clearance within hours of drug administration					Total not cleared
			24	48	72	96	120	Total	24	48	72	96	120	
P. vivax	4	3		1	1		1	4						4
P. falciparum	1	1		-	-		-	Nil						
Mixed P.v./P.f.	1	1	1/0					1						1

Pyrimethamine 25 mg given on two consecutive days was shown ineffective to clear asexual parasites in two out of 31 falciparum malaria cases (Jaswant Singh et al., 1952). Srivastava et al. (1953) showed that a single dose of 25 mg pyrimethamine failed to clear parasites in one out of 13 cases treated. Thus, the single dose of 25 mg of pyrimethamine was not completely effective.

In the present series, 12.5 mg of pyrimethamine combined with three levels of DDS dosages namely, 100, 50 and 25 mg were tried. The failure to clear asexual parasites in persons having vivax and falciparum infections (compiled from Tables 9, 12 and 15) was as given below:

Pyrimethamine 12.5 mg	Diamino-diphenyl-sulfone 100 mg	50 mg	25 mg
P. vivax	0/6	0/12	2/5
P. falciparum	0/6	0/7	0/2
Both infections	0/12	0/17	2/6

(Numerator = failures; denominator = number of infections treated)

A combination of 12.5 mg pyrimethamine with either 100 or 50 mg DDS was completely effective in 29 cases of vivax and falciparum malaria. In other words, a much smaller dose of each in combination was required for effective removal of asexual parasites than that needed with either given separately. This effect was further substantiated by the decline of parasite density indices recorded on five consecutive days as given below:

Regimen	Dosages and drugs (equivalent to adult dosage)	D day	D + 1 day	D + 2 day	D + 3 day	D + 4 day	D + 5 day
I	250 mg DDS	5.4	4.2	1.7	1.5	1.8	
II	200 mg DDS	7.3	3.5	1.5	1.4	1.0	1.0
III	100 mg DDS plus 12.5 mg pyrimethamine	6.8	4.1	0.5	0.0	0.0	0.0
IV	50 mg DDS plus 12.5 mg pyrimethamine	7.4	3.9	1.3	0.0	0.0	0.0
V	25 mg DDS plus 12.5 mg pyrimethamine	6.7	6.0	4.7	5.0	2.0	2.5

The comparatively smaller single doses (250 and 200 mg) of DDS were deliberately chosen to determine the smallest effective dose. The regimen I (250 mg DDS per adult) was found effective against P. falciparum in clearing the asexual parasites as well as fever in all cases within 72 hours. A single dose of 200 mg of DDS in children of Northern Nigeria was shown to clear asexual falciparum parasites within 96 hours (Archibald & Ross, 1960). In the present series age for age, the dosage used was almost half of that used in Northern Nigeria. The greater speed of action in the present series was of interest. It was noteworthy, however, that in a child aged three years with a mixed infection, the asexual parasites of P. falciparum were cleared within 24 hours; the same regimen was found inadequate in clearing the asexual parasites in three out of eight vivax infections (mixed infection included). The strain of P. falciparum appeared to be more sensitive to DDS than the strain of P. vivax. Similar higher sensitivity of the highly virulent (Nuri strain) P. knowlesi to DDS was noted where the minimum effective dose (MED) was found to be as low as 0.25 mg/kg compared to the MED against P. cynomolgi which was as high as 0.5 mg/kg (Ramakrishnan, Basu et al., 1961). The over-all failure of the regimen was seen in three cases out of the 12 treated and, therefore, 250 mg DDS as a single dose was not considered adequate for routine therapy.

The regimen II (200 mg DDS per adult) also proved effective in controlling both fever and parasitaemia due to P. falciparum; all the five cases (mixed infection included) showing such infection were free from fever as well as asexual parasites within 48-72 hours. But, the regimen failed to produce asexual parasite clearance in three out of nine vivax cases (mixed infection included). Thus, the over-all failure of the regimen irrespective of the types of infection was seen in three out of 12 cases treated and, therefore, was not found adequate for routine therapy.

The regimen III (100 mg DDS combined with 12.5 mg pyrimethamine per adult) proved effective in effecting clearance of asexual parasites of both species as well as termination of fever. The speed of action in respect of termination of fever was 48 hours in both types of infection. The speed of clearance of asexual stages of P. falciparum and P. vivax was 48 and 72 hours respectively. The clearance of P. vivax gametocytes also appeared to be quicker than with DDS alone due probably to the action of pyrimethamine on pregametocytes. No side effects were noted in the persons under this regimen.

DDS and pyrimethamine (100 and 12.5 mg respectively) also proved superior to regimen IV (50 and 12.5 mg respectively) in that the parasite density index showed greater decline in the former than in the latter. Judging by the speed of action, regimen III was found comparable to single dose therapy with 4-aminoquinoline group of drugs at a dosage level equivalent to 600 mg of the chloroquine base (Srivastava, 1953; Jaswant Singh, Ray & Misra, 1953). The well-known tardy action of pyrimethamine alone (Srivastava, 1953, and Chaudhuri, 1953) was markedly improved upon by this combination. Such a regimen would be four times less expensive than the single dose therapy with chloroquine.[1]

A lower dose combination of DDS and pyrimethamine (regimen IV - 50 and 12.5 mg respectively) also proved adequate and quick in both types of infection irrespective of the immunity factor. All the cases were rendered afebrile within 72 hours. The decline in PDI was slightly smaller than that in regimen III. A still smaller dose combination of the two drugs (regimen V) was found unsuitable for adoption as the failures were frequent.

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[1] Chloroquine 600 mg base - Rs 0.144 (US$ 0.67)
Pyrimethamine 25 mg - Rs 0.035 (US$ 0.15)
DDS 100 mg - Rs 0.020 (US$ 0.09)

Pyrimethamine 25 mg given on two consecutive days was shown ineffective to clear asexual parasites in two out of 31 falciparum malaria cases (Jaswant Singh et al., 1952). Srivastava et al. (1953) showed that a single dose of 25 mg pyrimethamine failed to clear parasites in one out of 13 cases treated. Thus, the single dose of 25 mg of pyrimethamine was not completely effective.

In the present series, 12.5 mg of pyrimethamine combined with three levels of DDS dosages namely, 100, 50 and 25 mg were tried. The failure to clear asexual parasites in persons having vivax and falciparum infections (compiled from Tables 9, 12 and 15) was as given below:

Pyrimethamine 12.5 mg	Diamino-diphenyl-sulfone 100 mg	50 mg	25 mg
P. vivax	0/6	0/12	2/5
P. falciparum	0/6	0/7	0/2
Both infections	0/12	0/17	2/6

(Numerator = failures; denominator = number of infections treated)

A combination of 12.5 mg pyrimethamine with either 100 or 50 mg DDS was completely effective in 29 cases of vivax and falciparum malaria. In other words, a much smaller dose of each in combination was required for effective removal of asexual parasites than that needed with either given separately. This effect was further substantiated by the decline of parasite density indices recorded on five consecutive days as given below:

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