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MEFLOQUINE CLINICAL TRIALS – THERAPEUTICAL EXPERIENCE WITH MEFLOQUINE ALONE AND COMBINATION (MSP) IN BRAZILIAN MALE SUBJECTS WITH FALCIPARUM MALARIA

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A multicentric trial was carried out at the Health Ministry's Clinical Pharmacology Unit in Belém, Brazil, to evaluate the tolerance, toxicity and efficacy of the new compound mefloquine in the treatment of multidrug resistant falciparum malaria.

The study involved Brazilian male subjects aged 18-55, from endemic malarial areas. After two days of basal clinical and laboratory investigations the subjects received mefloquine or comparison drugs. Following their administration, the patients were kept for two months in the ward for a detailed observation.

Both drugs were well tolerated and safe, but whereas the efficacy of mefloquine was 100% the comparative drugs were 75% (sulfadoxine + pyrimethamine) and 92% (S + P + Quinine, 3 days course) effective, respectively.

On the second part of the trial mefloquine was used in a fixed-dose combination with sulfadoxine + pyrimethamine (10:20:1) assumed to be able to delay the appearance of falciparum resistant strains to mefloquine. Using a similar design it was observed that both the combination (MSP) and the comparative drug (S + P) were well tolerated and safe.

Finally a dose-finding study showed that mefloquine combination was highly effective against resistant falciparum strains with a dose as low as two tablets (mefloquine 250mg, sulfadoxine 500mg and pyrimethamine 25mg per tablet).

In the fifties malaria seemed to be controlled in Brazil but at the end of the sixties the situation changed due to economical and administrative dificulties and the appearance of resistance of *P. falciparum* to 4-aminoquinoline compounds (Ferraroni et al., 1981; Lopez-Antunano & Wernsdorfer, 1979; Moore & Lanier, 1961; Rieckmann et al., 1974; Silva, 1961; Walker & Lopez-Antunano, 1968; Young & Moore, 1961 and Zu-Jie, 1981).

The aggravation of the situation with a reported resistance also to quinine and the fixed-dose combination sulfadoxine-pyrimethamine showed the need to develop a new effective drug or drug combination for the treatment of malaria due to resistant falciparum strains (Almeida Netto et al., 1972; Chongsuphajaisiddhi et al., 1981; Clyde et al., 1970; Neiva, 1910 and Reacher et al., 1981).

WHO/PAHO/TDR/UNDP/World Bank and the Health Ministries of the WHO Members decided to carry out multicentric trials with the new compound Mefloquine, a quinoline-methanol derivative developed at the Walter Reed Army Institute of Research in Washington, D.C. To avoid the appearance of resistance to mefloquine they also decided to try the fixed-dose combination mefloquine-sulfadoxine-pyrimethamine (MSP).

Extensive data on mefloquine antimalarial activity, animal pharmacology and toxicity have been published. Many investigators have reported on its effectiveness in human malaria, including that caused by multidrug resistant strains (Canfield & Heiffer, 1978; Desjardins et al., 1979; Doberstyn et al., 1979; Hall et al., 1977; Jiang et al., 1982; Rozman & Canfield, 1979; Souza, 1983a,b; Souza et al., 1985a,b; Tin et al., 1982; Trenholme et al., 1975 and Walter Reed Army Institute of Research, 1978).

In Brazil the first report about *P. falciparum* resistance to quinine appeared in 1910 (Neiva). In 1961, da Silva et al., reported falciparum resistance to chloroquine, confirmed later in 1968 (Walker; Lopez-Antunano). In the seventies many investigators in Brazil and overseas have reported the resistance of *P. falciparum* to sulfadoxine + pyrimethamine (de Almeida Netto, 1972; Reacher, 1981 and de Souza, 1983a,b).

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These clinical trials were developed in different phases (Phases I, II and III for Mefloquine alone and Phases I and II/III for the Combination), and the study was carried out in the Clinical Pharmacology Unit of the Health Ministry, at the Barros Barreto Hospital, in Belém, Pará State, in the period 1979-1984.

MATERIAL AND METHODS

Randomized and double-blind trials, using a "double dummy" system of drug administration, were adopted for the studies in all phases with 66 days for the control of the patients in the ward, except for phase III of the Mefloquine Trial that was developed as an open, randomized and prospective study with a total of 42 days observation period.

Selection of patients – The subjects were Brazilian males, aged 18-55, mostly from endemic malarial areas of Paragominas and Marabá (south of Pará State) that had not received any antimalarial drug for four weeks prior to admission to the study. The subjects did not suffer from severe infections or degenerative diseases nor presented serious cardiac or neurological problems. Informed consent was obtained and the patients were hospitalized in a special ward of the Barros Barreto Hospital for the duration of the study. Falciparum malaria transmission does not occur in Belém.

Drug administration – In phase I of Mefloquine (M) trial ten volunteers received a single oral dose of four tablets of Mefloquine 250mg plus two tablets of placebo resembling Fansidar R (S + P), and other ten volunteers received two tablets of S + P plus four tablets resembling M. The drugs were given under supervision, with a glass of water after a light breakfast.

In phase II of M trial fifty patients received a single oral dose of four tablets of M plus three tablets resembling S + P, and another group of fifty received three tablets of S + P plus four tablets of placebo resembling M, under supervision, with a glass of water, after a light breakfast.

Phase III of M trial was an open, randomized and prospective study and the drug were administered as follows: one group of fifty volunteers received four tablets of M as a single oral dose (M group) and another group of fifty received 600mg of quinine base each eight hours and three tablets of S + P four hours after the first dose of quinine on day 0, and 600mg of quinine at eight hours intervals on days 1 and 2 (S + P + Q group). The drugs were administered at convenient time according to patient situation and also under adequate supervision.

In phase I of the Combination Trial (MSP) a group of ten volunteers received three tablets of MSP (Mefloquine 250mg, sulfadoxine 500mg and pyrimethamine 25mg per tablet) plus three tablets of placebo resembling S + P, and another group of ten received three tablets of S + P plus three tablets of placebo resembling MSP. The drugs were administered under supervision.

Finally, in phase II/III of MSP trial, a dose-finding study, fifty patients received one tablet of MSP plus two tablets of placebo, fifty received two tablets of MSP plus one tablet of placebo and fifty received three tablets of MSP.

The subjects were admitted to the ward two days prior to the drug administration on day 0. The medical history was recorded and a complete clinical examination was performed, including physical examination, measurement of body weight and height, electrocardiogram (ECG) and chest X rays. Physical examinations were carried out daily, from day -2 to day 7, and then once a week until day 63.

Laboratory studies – Haematological studies included red blood cell (RBC) count, haemoglobin (Hb), erythrocyte volume fraction (haematocrit), total and differential white blood cell (WBC) counts, reticulocyte count and platelet count. Thick blood films were examined for malarial parasites.

Biochemical tests included serum levels of albumin, alkaline phosphatase, alanine amino transferase (SGPT), aspartate amino transferase (SGOT), bilirubin, calcium, chlorides, cholesterol, creatinine, glucose, iron, magnesium, phosphate, potassium, sodium, triglycerides and urea. Most of the haematological and biochemical assays were carried out on days -2, 0, 1, 4, 7, 14, 28 and 63.

Urine samples were tested for pH, albumin, glucose, haemoglobin and urobilinogen, and the sediment for casts, leukocytes, RBC, parasites, etc., on days -2 to 7 and 14, 21, 28 and 63. On day -2 urine samples were tested also for the presence of 4-aminoquinolines and sulfonamides.

Stool samples were examined for the presence of blood and parasites on days -2, 0, 4 and 7.

Blood drug levels – For phase I of Mefloquine and MSP (combination) trials, blood samples were collected for estimation of the drug level on days 0 to 7, 14, 21, 28, 35, 42, 49, 56

and 63. In all phases of Mefloquine and MSP trials blood samples were collected for estimating the drug plasma level in case of early vomit after drug administration and/or in case of recrudescence.

RESULTS

In the phase I studies of Mefloquine (M) and combination (MSP) trials, when the investigation looked mainly for tolerance and toxicity, none of the groups (M, MSP, and S + P) showed abnormalities in blood pressure, pulse rate and ECG throughout the study period. No significant respiratory system changes were observed in any group after drug administration. The same occurred in the other phases of the study (phases II and III of Mefloquine and phase II/III of combination trials).

There were no significant drug-related changes in the neuropsychiatric system in any group except that mild and transient dizziness was observed in all phases, usually in low percentage of cases, and none of the patients needed any specific treatment.

Body weight – In all phases of Mefloquine trials (alone or in combination) the body weight of all subjects were comparable at the beginning and at the end of the study and even a small overall gain was observed (Table I).

TABLE I

Body weight of Brazilian male patients of falciparum malaria from an endemic area, at the beginning and at the end of the study with mefloquine and mefloquine combination, 1979-1984.

Phase Trial	Group	Body weight, Kg (mean)		
		At beginning	At end	Overall gain
I Mefloquine	M	59,2	62,8	3,6
	S+P	55,7	60,3	4,6
II Mefloquine	M	56,1	60,4	4,3
	S+P	57,2	62,0	4,8
III Mefloquine	M	55,9	58,9	3,0
	S+P+Q	55,0	58,1	3,1
I Combination	MSP	57,9	61,0	3,1
	S+P	59,5	61,0	1,5
II/III Combination	MSP 1	57,0	61,3	4,3
	MSP 2	57,8	61,4	3,6
	MSP 3	57,7	61,7	4,0

Body temperature – In phases I of Mefloquine (M) and combination (MSP) trials almost all of the volunteers were negative for any kind of plasmodium, in spite of coming from endemic areas and for that reason just a few of them showed fever. In M group of Mefloquine trial the body temperature was high in two subjects on day 0, in one on day 1 and in three on day 4, while in S + P group two subjects had fever on day 0, three on day 1, two on day 2, one on day 3 and two on day 6. In the phase I of the combination study the body temperature was normal in all subjects from both groups throughout the observation period.

In phases II and III of Mefloquine trials and in phases II/III of combination trials (dose-finding) the volunteers were always positive for *P. falciparum* asexual forms, and consequently most of them presented fever in the period of days -2 to 7.

In the M group of phase II 22 patients had fever on day 0 and all were cleared by day 5. In the S + P group 17 subjects had fever on day 0 and 16 were cleared by day 5. Fever recurred in some patients on days 6 and 7 but 100% fever clearance was seen between days 14 and 28.

In phase III (Mefloquine trial), from 49 patients of M group 47 presented fever on day 0, 30 on day 1, 10 on day 2, two on day 3, one each on days 4 and 5, none on day 6 and one on day 7. In the S + P + Q group 47 of 50 subjects presented fever on day 0, 30 on day 1, nine on day 2, one on day 3, none on day 4, one on day 5, none on day 6 and one on day 7. In both groups we can assume that the fever clearance occurred by day 3 in view of the fact that in the patients that showed raised temperature this was very low (37,5°C).

In the phase II/III of the MSP (combination) trial (dose-finding study) the fever clearance occurred by day 4 in the group given one or two tablets, and by day 3 in the group given three tablets. In the first group fever recurred after day 21, nine subjects showing recrudescence.

Liver and spleen – Table II shows liver and spleen enlargement observed in patients of all phases of both Mefloquine and combination trials, but usually at the end of the observation period just a few of the subjects remained with hepatomegaly and/or esplenomegaly (small enlargement). According to the figures there was no significant difference between each group before and after drug administration.

TABLE II

Enlarged liver and spleen in Brazilian male patients of falciparum malaria from an endemic area before administration and at the end of trials with mefloquine and mefloquine combination, 1979-1984.

Phase / Trial	Group	Enlarged spleen		Enlarged liver	
		Beginning	End	Beginning	End
I	M	3	–	8	–
Mefloquine	S+P	3	–	5	–
II	M	39	9	30	1
Mefloquine	S+P	39	8	22	1
III	M	40	1	47	1
Mefloquine	S+P+Q	41	2	48	6
I	MSP	2		1	–
Combination	S+P	2	–	1	–
II/III	MSP 1	42	6	36	2
Combination	MSP 2	44	2	44	4
	MSP 3	41	1	41	4

Haematology – The volunteers of phase I of both trials for Mefloquine and combination, at the beginning and at the end of the observation period, showed normal blood values for the local standards, but presented some improvement in the parameters.

Many of the patients of phases II and III of the Mefloquine study and of the combination trial, that were positive for *P. falciparum* asexual forms, showed haemoglobin, RBC count and haematocrit below normal values before drug administration, but after treatment the parameters improved.

The total mean WBC count did not show significant difference in all phases of Mefloquine and combination trials, both at the beginning and at the end of the observation period. In the differential count most of the volunteers presented high eosinophilia probably due to helminth infection.

Reticulocyte and platelet counts were normal in all groups before and after drug administration.

Biochemical investigations – No significant drug-related changes were observed after the administration of Mefloquine, Mefloquine combination, sulfadoxine + pyrimethamine and sulfadoxine + pyrimethanine and sulfadoxine + pyrimethamine + quinine. In spite of some values appearing slightly above the normal range before the antimalarial drug administration, after the specific treatment they became normal (Table III).

TABLE III

Falciparum malaria patients with slight alterations in SGOT, SGPT and Bilirubin before treatment and that attained normal values after drug administration of mefloquine and combination trials, in Brazil, 1979-1984.

Phase / Trial	Group	SGOT	SGPT	Bilirubin
I Mefloquine	M	2 (10)*	4 (10)	– (10)
	S+P	3 (10)	4 (10)	1 (10)
II Mefloquine	M	7 (49)	3 (49)	– (49)
	S+P	6 (48)	4 (48)	1 (48)
III Mefloquine	M	4 (50)	8 (50)	3 (50)
	S+P+Q	4 (50)	10 (50)	3 (50)
I Combination	MSP	– (10)	– (00)	– (10)
	S+P	– (10)	– (00)	– (10)
II/III Combination	MSP 1	14 (50)	11 (50)	8 (50)
	MSP 2	16 (50)	17 (50)	10 (50)
	MSP 3	12 (50)	18 (50)	12 (50)

*Between brackets the total number of subjects involved in the study.

Urine examinations – The volunteers of phase I of Mefloquine and combination trials showed no significant changes in urinary parameters either before and after drug administration.

In phases II and III of Mefloquine and in phase II/III of combination trials all patients presenting *P. falciparum* infection with at least 400 asexual forms/mm^3 of blood, showed the presence of protein and urobilinogen in the urine in the early stages of the study, with some correlation between the intensity of the abnormality and the grade of the infection. After the antimalarial drug administration the urinary alteration disappeared within the first week.

Stool examination – More than 90% of all volunteers showed one or more species of helminth, sometimes associated with protozoan infections *(E. histolytica* and *G. lambia).*

Parasitological response – In phases I of Mefloquine and combination trials the objectives were basically the determination of the tolerance and the toxicity of the new drug alone or in combination and its pharmacokinetics behavior.

The volunteers of the M group of phase I according to their parasitological findings were distributed as follows: three subjects were positive for *P. falciparum* and two for *P. vivax* on day 0. After treatment all cleared by day 2. No recrudescence was observed but four cases of relapses due to *P. vivax* occurred. Among the volunteers of S + P group, six subjects had positive smears for asexual forms of *P. falciparum* and two for *P. vivax* on day 0. After treatment of the falciparum cases one cleared on day 1, four on day 2 and one on day 5. Three cases of recrudescence occurred (two delayed and one early). Four cases of relapse due to *P. vivax* were recorded.

In phase II (M trial), besides following the observation of tolerance and toxicity to the drugs, the most important datum to be observed was the parasitological response. In the M group, of 49 patients 44 cleared by day 3 (90%) and all on day 6, and in the S + P group of 48 patients 38 cleared by day 3 (79%), but at day 7 four patients still remained positive (three RII and one RIII).

At the end of the observation period the M group showed a cure rate of 100%, with relapses due to *P. vivax* in 11 cases. For S + P group the cure rate was 75% (36 patients showed S response, eight RI, three RII and one RIII responses); relapses due to *P. vivax* occurred in 15 cases.

Phase III of Mefloquine trial compared the action of the drug in patients during an acute attack. From 49 volunteers that received Mefloquine 42 cleared by day 4, while from 50 treated with S + P + Q 43 cleared by the same day. At the end of the observation period all patients of M group were cured, but four patients of S + P + Q group showed recrudescence (92% cure rate). In M group two cases had relapses due to *P. vivax*, while in S + P + Q group relapses occurred in seven.

The dose – finding trial for Mefloquine combination (MSP) involved 150 volunteers, both oligosymptomatic and in acute attack in three groups of 50, each receiving one, two or three tablets, respectively. In the first group there were two dropouts and from the 48 that completed the observation period nine showed recrudescence after all had cleared by day 5.

In the second group there was one dropout and from the 49 that remained till the end of the observation period 43 cleared by day 3 and all by day 7; no recrudescence appeared in this group. Finally in the group three there was one dropout and from the remaining 49, 43 cleared by day 3 and all by day 6. The cure rate was 100%. Relapses due to *P. vivax* occurred in all groups: 18 cases in group 1 between days 14 and 63, 19 cases in group 2 between days 35 and 63 and 16 cases in group 3, between days 35 and 63 (Table IV).

TABLE IV

Summary of parasitological responses of falciparum malaria patients to mefloquine (M) and mefloquine combination (MSP) in comparison with sulfadoxine+pyrimethamine (S+P) and sulfadoxine+pyrimethamine+quinine (S+P+Q), 1979-1984.

Phase	Group	Standard test (7 days)		Extended test (63 days)				Cure
Trial		Cleared	Uncleared	S	RI	RII	RIII	Rate, %
I	M	3	–	3	–	–	–	100
Mefloquine	S+P*	6	–	3	3	–	–	50
II	M	49	–	49	–	–	–	100
Mefloquine	S+P	45	4	36	8	3	1	75
III**	M	49	–	49	–	–	–	100
Mefloquine	S+P+Q	50	–	46	4	–	–	92
I	MSP	1	–	1	–	–	–	100
Combination	S+P	2	–	1	1	–	–	50
II/III	MSP 1	48	–	39	9	–	–	81
Combination	MSP 2	49	–	49	–	–	–	100
	MSP 3	49	–	49	–	–	–	100

*2 Tablets
**Observation period = 42 days.

Gametocytes were seen in about 70% of the falciparum malaria carriers in both Mefloquine and mefloquine combination trials (a total of 360 patients in all phases) and their disappearance occurred progressively during the observation period (Table V).

TABLE V

Gametocyte population in differents time of the observation period, in mefloquine and combination trials, in Brazilian male patients with falciparum malaria, 1979-1984.

Phases		Subjects with gametocytes on day						
	Group							
Trial		0	7	21	28	35	42	63
I	M	3	3	3	1	–	–	–
Mefloquine	S+P	4	4	4	1	1	1	–
II	M	31	38	27	8	4	1	–
Mefloquine	S+P	35	48	32	20	12	6	2
III	M	21	32	7	4	–	–	–
Mefloquine	S+P+Q	26	39	23	15	4	–	–
I	MSP	1	–	–	–	–	–	–
Combination	S+P	4	2	2	2	1	1	–
II/III	MSP 1	43	45	23	8	1	5	–
Combination	MSP 2	40	40	19	9	3	–	–
	MSP 3	43	43	27	13	1	–	–

Side-effects – The incidence of side-effects occurring within four days of drug administration is seen in Table VI but we need to take into consideration the fact that all the patients of phases II and III of Mefloquine trial and of phase II/III of combination trials when selected for the study, had positive smears for *P. falciparum* asexual forms and most of them had fever, sometimes high. Malarial fever is itself associated with headache, nausea, vomiting, dizziness and often abdominal pain, making it difficult to differentiate between disease symptoms and drug-induced side-effects.

TABLE VI

Side-effects observed within four days after drug administration in all phases of both mefloquine and mefloquine combination trials in brazilian male patients of falciparum malaria, from an endemic area, 1979-1984.

Phases / Trial	Group	% of symptoms observed after drug administration within four days						
		Abdominal Pain	Diarrhoea	Nausea	Vomiting	Headache	Dizziness	Tinnitus
I	M	–	20	10	–	30	40	–
Mefloquine	S+P	–	–	10	–	50	20	–
II	M	–	31	47	18	57	63	–
Mefloquine	S+P	–	19	31	8	63	52	–
III	M	16	24	12	12	–	16	–
Mefloquine	S+P+Q	4	16	48	28	–	20	34
I	MSP	–	–	30	–	–	20	–
Combination	S+P	10	–	30	10	–	20	–
II/III	MSP 1	2	17	15	2	–	0	–
Combination	MSP 2	6	14	14	4	–	10	–
	MSP 3	10	16	31	16	–	8	2

DISCUSSION

In this study the phase I of Mefloquine and combination trials were performed in volunteers with previous experience of malaria, multiple helminth infection, ânaemia, defective nutrition and enlarged livers and spleens as representatives of a target population.

For phases II and III of Mefloquine trial and phase II/III of combination trial the volunteers were selected from the same target population except for the obligatory presence of *P. falciparum* in a concentration of at least 400 asexual forms/mm^3 of blood.

In phase I of Mefloquine trial, Mefloquine given as a single oral dose of 1000mg, was compared with standard antimalarial, sulfadoxine-pyrimethamine, for tolerance and safety in adult Brazilian male subjects from an endemic area.

The method of selection explains the low body weight, low values for RBC count, Hb, haematocrit, iron serum, plasma protein and high eosinophil count. Some volunteers also had enlarged liver and spleen and slightly raised SGOT and SGPT.

Mefloquine was well tolerated and in all cases RBC count, Hb, haematocrit and body weight improved during the trial, probably due to better food and hygiene conditions.

P. falciparum and *P. vivax* infections both cleared within 24 hours after drug administration in the phase I of Mefloquine trial in volunteers of M group; there was no recrudescence of *P. falciparum* but relapses due to *P. vivax* occurred in four cases. For the subjects given S + P the total parasite clearance occurred by day 6, but recrudescence appeared in three cases due to *P. falciparum* and relapses due to *P. vivax* were observed in four volunteers.

Nausea, dizziness, diarrhoea and headache were the side-effects observed but the symptoms were mild to moderate and transient and did not need any specific treatment in both groups. Dizziness and diarrhoea were higher in patients given Mefloquine.

In phase I of combination trial, MSP given as a single oral dose (Mefloquine 750mg, sulfadoxine 1500mg and pyrimethamine 75mg) was compared with a standard antimalarial, sulfadoxine-pyrimethamine, for tolerance and safety, in adult Brazilian males from endemic areas. Most of them were invited to participate in the study after antimalarial treatment as inpatients and consequently showed better conditions than those coming straight from the field.

MSP has been found to be safe and well tolerated. The side-effects observed were mild or moderate and transient and did not require specific treatment. The same occurred in the group given sulfadoxine-pyrimethamine.

Haematological, biochemical and urine tests showed no adverse effects after Mefloquine, MSP and sulfadoxine-pyrimethamine administration. Clinical parameters, lung X rays and ECG studies showed that Mefloquine, MSP and sulfadoxine-pyrimethamine were well tolerated.

Besides looking for tolerance and safety of the drugs in phases II and III of Mefloquine trial and phases II/III of combination trial, the most important objective of these phases was the observation of the efficacy to clear the falciparum asexual parasites.

In phase II Mefloquine given as a single oral dose of 1000mg was compared to a standard antimalarial S + P, in oligosymptomatic carriers of *P. falciparum* infections with at least 400 asexual forms/mm^3 of blood.

The incidence of side-effects was comparable in both groups and probably was influenced by the presence of fever developed in many subjects before drug administration. The side-effects were transient and did not require any specific treatment. Neither Mefloquine nor sulfadoxine-pyrimethamine produced any adverse reactions on the haematopoietic system or on liver or kidney functions.

Clinically there was no significant difference in the tolerance and safety of both drugs, however Mefloquine was more effective producing 100% of S type responses compared with 73% of sulfadoxine-pyrimethamine eight RI, three RII and one RIII responses). This study showed that some *P. falciparum* strains of Pará State developed resistance to S + P.

In phase III Mefloquine given as a single oral dose of 1000mg was compared with standard regimens of quinine plus sulfadoxine-pyrimethamine, given over a period of three days, for the treatment of acute attack of falciparum malaria. The observation of the side-effects was hampered by the high intensity of the clinical findings due to the disease but it was possible to determine that abdominal pain and diarrhoea were higher in the Mefloquine group and nausea, vomiting and tinnitus in the sulfadoxine-pyrimethamine + quinine group. All side-effects were mild or moderate and transient and did not require specific treatment.

The rate of fever clearance was not significantly different in both groups and the parasitological cure rate showed 100% of S responses for Mefloquine and 92% for the sulfadoxine-pyrimethamine + quinine group that had four cases of RI responses.

Neither Mefloquine nor sulfadoxine-pyrimethamine + quinine produced any adverse effects on the haematopoietic system or liver and kidney functions.

Finally the dose-finding study performed with MSP compared three levels of doses, given as single oral doses of one tablet, two tablets and three tablets, of a combination of Mefloquine 250mg, sulfadoxine 500mg and pyrimethamine 25mg per tablet. Each group included 50 volunteers suffering of falciparum malaria and the subjects were oligosymptomatic or polysymptomatic (acute attack) patients.

In spite of the presence of the symptoms of the disease, sometimes with high intensity, it was possible to observe some side-effects that were comparable in all groups, except for abdominal pain and vomiting that rose according to the increase in dose of the drug. Anyway these side-effects were mild or moderate and transient.

MSP did not produce any adverse effect on the haematopoietic system or on liver or kidney functions as revealed by the biochemical, haematological and urinary tests.

There was no significant difference in the fever and parasite clearance time between the three groups but while the patients given two and three tablets showed 100% of S responses, those given just one tablet showed a cure rate of 79% (nine RI responses).

In view of the general results it seems that both Mefloquine and Mefloquine combination were ineffective against falciparum gametocytes. Consequently to prevent malaria transmission a complementary treatment with primaquine (0,75mg/kg of body weight) will be necessary.

CONCLUSIONS

In this study of tolerance and safety of Mefloquine and Mefloquine combination (phases I of both trials) and tolerance, safety and efficacy of Mefloquine and MSP (phases II and III of M trial and phase II/III of MSP trial) in Brazilians adult males from malaria endemic areas it has been found that:

1 – Mefloquine was safe and well tolerated at the dose of 1000mg.

2 – Mefloquine produced 100% cure rate in carriers of falciparum malaria, whereas sulfadoxine-pyrimethamine showed 75% and sulfadoxine-pyrimethamine + quinine 92% of cure rate in the same conditions.

3 – Mefloquine in a fixed-dose combination (Mefloquine 10 + sulfadoxine 20 + pyrimethamine 1) was safe and well tolerated up to the dose of three tablets.

4 – Mefloquine combination produced 100% cure rate in doses of two and three tablets.

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