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EPIDEMIOLOGICAL DISTRIBUTION OF *PLASMODIUM FALCIPARUM* DRUG RESISTANCE IN BRAZIL AND ITS RELEVANCE TO THE TREATMENT AND CONTROL OF MALARIA

JOSÉ MARIA DE SOUZA

Núcleo de Patologia Regional e Higiene, Univ. Fed. do Pará, Av. Generalíssimo Deodoro, 92, 66055-240 Belém, PA, Brasil

With the use of a simple formulary, filled by health agents was established a monitoring programme for responses of P. falciparum *to the antimalarial drugs. This monitoring programme is emphasized for the knowledge of the epidemiology of the drug resistance and the control of malaria falciparum in Amazon Basin where occurs more than 95% of Brazilian malaria cases every year. It was demonstrated that still now 4-aminoquinolines have a great importance for the mortality control in areas where just SUCAM (National Health Foundation - Health Ministry) agenst are present without any medical assistance. The results obtained permitted the simplication of malaria treatment in Brazil. Important conclusions were established in the field of malaria drug resistance.*

Key words: *Plasmodium falciparum* – drug resistance – epidemiology – Brazil

Neiva (1910) was probably the first to describe drug-resistance in malaria when he reported difficulty in curing falciparum malaria with quinine. Forty-five years later two physicians in Amazônia reported the same fact with the new drug chloroquine that was not able to cure some cases of malaria due to *Plasmodium falciparum* in the Federal Territory of Guaporé (actual Rondônia State) (Brito & Pinheiro, 1954).

While Brito & Pinheiro presented their results in a National Medical Meeting after reporting the occurrence to the Health Secretary of the Federal Territory of Guaporé without great repercussion, Moore & Lanier (1961) and Young & Moore (1961) published in an very important international scientific periodical their observations about the presence of chloroquine-resistant *P. falciparum* strains in the region of Madalena River in Colombia. In the same year Silva and colleagues published two articles about the resistance of *P. falciparum* to chloroquine in Brazil (Silva 1961; Silva et al., 1961).

In the sixties several authors in South America and in Asia reported the occurrence of falciparum malaria resistance to chloroquine and amodiaquine and underlined their preoccupation with the spread of drug resistant parasites and the deterioration of the malaria eradication and control programmes through the intensification of drug resistance (Bustamante, 1959; Clyde, 1960; Keer et al., 1961; Comer et al., 1968).

The appearance and spread of 4-aminoquinoline resistant strains of *P. falciparum* lead to the search for new drugs and the combination sulfadoxine + pyrimethamine (S + P) was tried for the first time in our country by Walker & Lopez Antuñano in the beginning of the sixties with very good results which made possible the use of this combination in the field in the seventies (Walker & Lopez Antuñano, 1968). Unfortunately, very early in its use, the appearance of resistant strains of *P. falciparum* to S + P was reported in Brazil and other countries (Almeida Netto et al., 1972; Espinal et al., 1981; Alecrim et al., 1982; de Souza et al., 1985). In the lst National Malaria Conference in Thailand, 1980, it was reported that in 1970 the combination S + P cured 90% of malaria falciparum cases but in 1979 the cure rate fell to 10%.

In Brazilian Western-Amazônia the resistance to the combination S + P was described in very high intensity and with a very low cure

rate (about 30%) in the beginning of the eighties (Alecrim et al., 1982). At the same time in the Eastern-Amazonia this combination showed a cure-rate of 75%, but this efficacy fell quickly since in 1981 the total resistance was 25% (mainly RI cases) and in 1984 it rose to 60% and finally in 1987 it was no less than 90% (de Souza, 1983, 1986; de Souza et al., 1988).

MONITORING PROGRAMMES

For several years we claimed the need for a special monitoring programme to follow the spread to the *P. falciparum* drug resistance but in spite of the suggestion of many experts in malaria control programs and the recommendation of Official Institutions like PAHO/WHO only in April, 1987 was it possible to establish an official MONITORING PROGRAMME OF *P. FALCIPARUM* RESPONSES TO THE DRUGS USED BY SUCAM IN AMAZONIA (ODRMP).

This programme (ODRMP) was started in Belém and Marabá, Pará State in July/1987 and in Goiânia, Goiás State in December, 1987. Unfortunately it was not possible to encourage all the SUCAM Regional Offices to establish the programme at the same time. Amapá State started the monitoring programme in 1989 and Acre State in 1990. Until now it was not possible to establish the official monitoring programme (ODRMP) in the states of Amazonas, Rondônia, Mato Grosso, Tocantins and Maranhão.

The resistance monitoring programme was conducted by health agents and supervised by inspectors and/or high level technicians. A clinical pharmacologist was the general advisor of the programme. Special formulary was routinely filled by health agents and in special cases by physicians. Information was obtained by the monitoring programme developed in Pará and Goiás States in the period 1987/1988 as follows:

1) The cases treated in Marabá and Belém came almost 100% from Pará and Amapá States (Tables I, II).

2) In Goiânia the observations showed that 70% of the patients came from Rondônia and Mato Grosso States (Table III).

3) The patients treated in Marabá showed parasite clearance in 70% of the cases but the cure rate was less than 20% for chloroquine, amodiaquine and the combination S + P. Consequently the occurrence of RII and RIII cases was low.

4) For the patients treated with chloroquine, amodiaquine and the combination S + P in Belem and Goiânia, the responses showed a parasite clearance of 50% and a cure rate less than 10% in Belem and less than 20% in Goiânia. The RII and RIII responses were about 40%.

5) When the drugs used were quinoline-methanol (mefloquine alone and/or quinine alone or in association with S + P or tetracycline), the parasite clearance was 100% in most cases in Belém, Marabá and Goiânia.

6) The cure rate of quinine alone (quinine sulphate 25mg/kg of body weight/day per 10 days) was about 80% and for mefloquine alone (16mg/kg of body weight in a single dose) was 100% in Belém, Marabá and Goiânia.

7) The 5 responses for the patients treated in Belém, Marabá and Goiânia with quinine (quinine sulfate 30 mg/kg of body weight/day per 3 days) + Sulfadoxine + Pyrimethamine (Standard dose) were 45/50% and for quinine (quinine sulfate 30 mg/kg of body weight/day per 3 days) + tetracycline (25 mg/kg of body weight/day per 7 days) were 95/100%.

8) Itaituba, Pará State municipality was the place that gave the most important contribution in number of patients treated in Belém, Marabá and Goiânia and in this way this municipality represented the most important source of spread of resistant strains according to the monitoring programme data, in view of the fact that the carriers of gametocytes may contaminate the malaria vectors.

9) Among the benefits obtained with the establishment of this monitoring programme in Belém, we may signal the diminution of the morbidity and the absence of mortality except when the patient did not procure SUCAM or was admitted in a hospital without good training in diagnosis and treatment of malaria.

10) The results obtained through the monitoring programme in Belém, Marabá and

TABLE I

Epidemiological distribution of *Plasmodium falciparum* resistance in patients treated in Belém, according to their origin and the type of response to the drugs used by Health Ministry (SUCAM) - July 87 - December 88

Drug used	State of origin (Municipalities)	Type response and number of cases						
		S	S/RI	RI	RII	RIII	U	I
Amodiaquine	Amapá (3)	2	4	15	11	1	3	–
	Pará (12)	–	2	21	22	–	–	1
	Amazonas (1)	–	1	–	–	–	–	–
	M. Grosso (1)	–	1	–	–	–	–	–
	Randônia (1)	–	–	1	–	–	–	–
	Roraima (1)	–	–	–	1	–	–	–
Chloroquine	Amapá (1)	–	–	–	1	–	–	–
	Maranhão (1)	–	1	–	1	–	–	–
	Pará (9)	1	1	15	13	–	1	–
	M. Grosso (1)	–	–	–	2	–	–	–
Sulfadoxine+ Pyrimetamine	Amapá (2)	2	–	9	9	2	–	–
	Maranhão (1)	–	–	–	2	–	–	–
	Pará (7)	1	2	8	11	3	–	–
(S + P)	Amazonas (1)	–	–	1	1	–	–	–
	M. Grosso (2)	–	–	–	1	1	–	–
Quinine + S + P	Amapá (3)	3	9	11	1	–	4	–
	Pará (15)	11	25	29	3	–	2	2
	M. Grosso (1)	–	1	1	–	–	–	–
	Randônia (1)	2	–	–	–	–	–	–
Quinine +	Amapá (3)	15	5	3	–	–	–	–
	Pará (7)	24	11	–	–	–	–	–
Teatracycline	Amazonas (1)	1	–	–	–	–	–	–
	M. Grosso (2)	3	2	–	–	–	–	–
Quinine alone	Amapá (3)	5	9	3	–	–	–	–
	Maranhão (1)	1	–	–	–	–	–	–
	Pará (9)	17	9	4	3	–	–	–
	M. Grosso (1)	–	1	–	–	–	–	–
Mefloquine	Amapá (2)	3	1	–	–	–	–	–
	Pará (1)	9	4	–	–	–	1	–

Goiânia in the period 1987/88 were fundamental to get the decision to withdraw the combination Sulfadoxine + Pyrimethamine from the regular SUCAM use and to simplify the therapeutics of malaria by SUCAM personnel (Manual de Terapêutica de Malária - 1990).

MALARIA CONTROL

With the decision to change our malaria programme from eradication to control, the *P. falciparum* resistance monitoring programme became a very important tool in the rational

TABLE II

Epidemiological distribution of *Plasmodium falciparum* resistance in patients treated in Marabá, according to their origin and the type of response to the drugs used by Health Ministry (SUCAM) - July 87 - December 88

Drug used	States of origin (Municipalities)	Type of response and number of cases						
		S	S/RI	RI	RII	RIII	U	I
Amodiaquine	Pará (9)	–	2	23	9	1	–	
	M. Grosso (1)	–	2	–	1	–	–	
Chloriquene	Amapá (1)	1	–	3	–	–	–	
	Pará (5)	5	5	14	8	–	–	
	M. Grosso (1)	–	–	–	2	–	–	
Sulfadoxine + Pyrimetamine (S + P)	Maranhão (1)	–	–	1	–	–	–	
	Pará (5)	4	6	13	13	4	–	
Quinine + S + P	Amapá (2)	–	2	1	–	–	–	
	Pará (7)	8	15	21	–	2	1	2
	M. Grosso (2)	–	1	1	–	–	–	
Quinine + Tetracycline	Maranhão (1)	1	–	–	–	–	–	
	Pará (5)	18	7	3	–	–	–	
Quinine alone	Amapá (1)	–	–	–	–	–	–	1
	Pará (2)	2	2	4	–	–	–	1
Mefloquine	Pará (2)	9	7	–	–	–	–	
	M. Grosso (1)	2	–	–	–	–	–	

drug use in the Amazon area. Thus we require the establishment of the ODRMP at least in the areas where the transmission is high and where the occurrence of severe cases is more frequent, with teams of health people well trained and convinced of the importance of this programme to know the behavior of malaria parasites for each drug used.

Another very important point is the need for the introduction of new antimalarial drugs as alternative weapons for the treatment of multidrug resistant strains of *P. falciparum.* Short course schemes to facilitate the use in the field in substitution to 4-aminoquinolines are preferred mainly because we know that quinine needs long course administration and produces many side effects and mefloquine has a very long half-life of elimination with the possibility of selection of resistant strains.

Finally the control of malaria has a correlation with the knowledge of the epidemiological configuration of the drug resistance of the parasites in a specific area in view of establishing the strategy of each local action programme.

CONCLUSION

In conclusion we emphasize:

a) The feasiblity of the establishment of a ODRMP.

b) The training of intermediate and high level health personnel for the improvement of this monitoring programme.

c) The need for governmental an non-governmental health organizations to work together

TABLE III

Epidemiological distribution of *Plasmodium falciparum* resistance in patients treated in Goiânia, according to their origin and the type of response to the drugs used by Health Ministry (SUCAM) - July 87 - December 88

Drug used	State of origin (Municipalities)	Type of response and number of cases						
		S	S/RI	RI	RII	RIII	U	I
Amodiaquine	Amapá (1)	–	–	–	–	1	–	–
	Pará (4)	2	1	4	7	1	2	–
	Goiás (2)	–	1	–	1	–	–	–
	M. Grosso (3)	2	2	5	2	2	2	–
	Rondonia (2)	3	–	1	–	–	1	1
Chloroquine	Pará (4)	2	1	9	2	2	3	–
	Acre (1)	–	–	–	1	1	1	1
	Amazonas (2)	–	–	1	–	1	–	–
	M. Grosso (3)	3	2	9	6	–	9	–
	Rondônia (3)	–	1	2	2	–	1	–
Sulfadoxine + Pyrimetamine (S + P)	Pará (4)	1	1	1	6	–	3	–
	Goiás (2)	1	–	–	–	1	–	–
	M. Grosso (5)	3	4	2	8	–	2	–
	Rondônia (3)	1	2	–	1	1	1	–
Quinine + S + P	Amapá (1)	–	2	–	–	–	4	–
	Pará (7)	12	14	15	1	–	3	–
	Acre (2)	–	2	–	–	–	1	–
	Amazonas (1)	–	1	1	–	–	–	–
	Goiás (3)	1	1	2	–	–	–	–
	M. Grosso (4)	9	21	17	4	–	1	–
	Randônia (5)	1	9	5	2	–	2	–
Quinine + Tetracycline	Amapá (1)	–	1	–	–	–		
	Pará (5)	12	9	–	–	–	1	1
	Amazonas (1)	1	1	–	–	–	–	–
	Goiás (3)	2	1	–	–	–	–	–
	M. Grosso (4)	21	12	–	–	–	–	–
	Randônia (1)	5	5	–	–	–	2	–
	Roraima (1)	–	1	–	–	–	–	–
Quinine alone	Amapá (1)	–	1	–	–	–	–	–
	Pará (5)	7	10	2	2	–	–	–
	Goiás (3)	–	2	–	1	1	–	–
	M. Grosso (3)	11	7	5	1	–	–	–
	Randônia (3)	2	4	–	–	–	–	–
Mefloquine	Pará (5)	2	–	–	–	–	–	–
	M. Grosso (2)	6	–	–	–	–	–	–
	Randônia (1)	2	–	–	–	–	–	–

for malaria control through a well established drug resistance monitoring programme.

d) The ODRMP is a very important tool in the permanent evaluation of the epidemiological configuration of the drug resistance in malaria parasites.

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